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TRAUMATIC NECROSIS OF PRETIBIAL MUSCLES*

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AN UNUSUAL case in which the pretibial muscles of both legs became acutely swollen, painful and paralyzed after a period of vigorous activity was recently observed on one of the medical wards of the Boston City Hospital. The clinical features were puzzling, and it was only after a biopsy had disclosed hemorrhage and necrosis that a clue to the nature of this disorder was obtained. Since we were unfamiliar with this condition and are unable to find verification of exactly similar cases in the medical literature, the following case is reported.

CASE REPORT

S. T., a 24-year-old man, who had emigrated from Greece less than a year before, could not express himself well in English, and the history was therefore obtained through an interpreter.

It was learned that his general health had always been good. His only important illness in the past had been malaria 2 years before entry, which had been treated by intramuscular injections of an unknown medicine. The only other item of possible interest was an easy fatigability of the legs, which had been present for the past year. The patient denied the ingestion of pork. Ten days before admission to the hospital he had had a sore throat and hoarseness from which he had recovered within 24 to 48 hours without interruption of his work as a bus boy.

At about 2 p.m. on May 19, 1947, he had competed with two companions in broad jumping on a cement pavement. Later during the same evening he began to experience sharp pains in both legs, and there was tenderness of the muscles from knees to ankles. He felt feverish, had general malaise and, after a restless night, was admitted to the hospital.

Physical examination disclosed a patient whose face was flushed and who was suffering considerable pain. He was alert and co-operative. Oral hygiene was poor, and one tonsil was enlarged and red. There was a Grade I apical systolic murmur. The heart and lungs were not remarkable. The liver and spleen could not be palpated. The patient lay with his legs flexed at hips and knees. The skin over the anterior surface of both legs from knees to ankles was pink and distinctly warmer than elsewhere. We examined the patient at this time and noted that all the muscles in the anterior tibial compartment were very firm and exceedingly tender. There was foot drop bilaterally and complete paralysis of the anterior tibial, extensor digitorum longus and extensor hallucis longus muscles. Passive flexion or extension of the feet at the ankles was painful. The peroneal, gastrocnemius and other muscles in the legs and thighs contracted normally and were not tender. The joints were neither swollen nor tender, and no thrombosed veins could be felt. There was slight hyperalgesia over the erythematous skin surface. The knee and ankle jerks were present, and the plantar reflexes were flexor bilaterally. Vibratory and position senses in the feet were normal. Pulsations were felt in the dorsalis pedis and posterior tibial arteries.

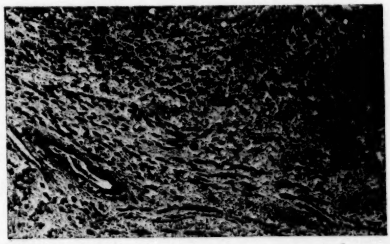

FIGURE 1. *Right Anterior Tibial Muscle Seventeen Days after Injury (x 50).*

Regenerating muscle fibers and remnants of necrotic muscle are widely separated by proliferating fibrous connective tissue, in which lymphocytes, plasma cells and macrophages are seen.

The temperature was 100.8°F., the pulse 84, and the respirations 22. The blood pressure was 128/88.

At the time of entry the urine was normal, but on the 3rd and 5th hospital days it gave +++ and ++ tests for albumin respectively. The white-cell count was initially 10,800, with 85 per cent neutrophils, 14 per cent lymphocytes and 4 per cent monocytes. Subsequently it was 8050, with a normal differential, except on the 6th hospital day, when there was an eosinophil count of 4 per cent. The hemoglobin was 14 gm. per 100 cc. The nonprotein nitrogen and fasting blood sugar were within normal limits. The stool was negative for blood and parasites. The blood Wassermann, Hinton and gonococcus complement-fixation tests were all negative. The skin test with trichina antigen gave no reaction. The concentrations of creatine and creatinine in the blood and urine were normal. The cerebrospinal fluid was examined twice, each time being entirely within normal

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limits. X-ray films of the chest and legs disclosed no abnormalities. Watson's test for porphyrins in the urine was negative. An electrocardiogram was normal.

On the 3rd hospital day the temperature rose to 102.4°F., and the patient appeared quite uncomfortable. Penicillin

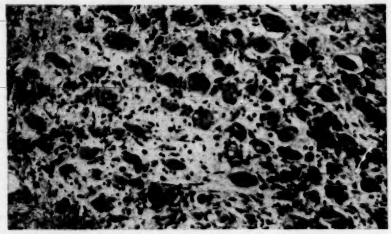

FIGURE 2. *Cross-Section from the Area Demonstrated in the Upper Part of Figure 1, showing the Rounded Contours, Occasional Vacuolization and Hyperplasia of Muscle Nuclei in the Remaining Fibers (x 200).*

was then given intramuscularly in doses of 25,000 units every 3 hours. The temperature gradually subsided over a period of 4 days. The leg muscles remained hard and indurated but were less tender, and the pretibial erythema gradually faded. By the 14th hospital day the patient was feeling quite well though foot drop and paralysis of the extensor muscles of the feet and toes continued. Tests of the electrical excitability of these muscles showed no reaction to either faradic or galvanic stimulus. On the 17th hospital day a biopsy of the upper part of the anterior tibial muscle of the right leg was performed. From this a diagnosis of traumatic myopathy was made. Improvement in the patient's general condition continued, but when he was discharged after 27 days in the hospital, the anterior tibial muscles were still paralyzed.

FIGURE 3. *Longitudinal Section of Muscle (x 50).*

The fibers in the center of the field, which are necrotic, are stained a bright red, are homogeneous and lacking in either transverse or longitudinal striations and are cracked transversely. In the lower margin active phagocytosis of the degenerated muscle fibers is demonstrated.

Several small pieces of the right anterior tibial muscle were excised, fixed in Zenker's solution and stained with phloxine and methylene blue, and phosphotungstic acid hematoxylin.

Some of the pieces contained apparently normal muscle fibers, whereas in others the normal skeletal muscle architecture was severely disrupted and there was a marked fibrous tissue replacement (Fig. 1 and 2). In these areas, muscle fibers were observed in all stages of degeneration. Some were swollen, intensely acidophilic and devoid of nuclei and striations; others were granular and vacuolated,

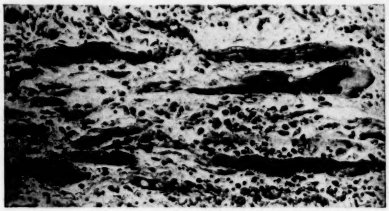

FIGURE 4. *Longitudinal Section of a Part of the Muscle that is Undergoing Regeneration (x 200).*

There are rows of muscle nuclei in the fibers. The fiber in the right upper corner has acquired transverse and longitudinal striations. The fibroblasts and interstitial cellular reaction consisting of macrophages, lymphocytes and plasma cells are demonstrated.

and their nuclei were shrunken and pyknotic. In two places the general architecture of a fasciculus could be distinguished. In these the central portion of each fasciculus was necrotic, consisting of swollen eosinophilic fibers with frequent transverse fissures and shrunken pyknotic nuclear remnants

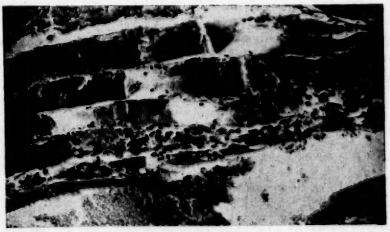

FIGURE 5. *Higher Magnification of the Lower Part of the Field Demonstrated in Figure 3, Showing the Necrotic Muscle Fibers and Their Removal by Macrophages (x 200).*

(Fig. 3). The connective tissue appeared to be inactive. At the borders of each fasciculus extensive regenerative activity was evident (Fig. 4). The muscle fibers in this region were small, and contained large numbers of well stained muscle nuclei. Longitudinal splitting was commonly observed, and the sarcoplasm had a well developed longitudinal striation. In one fasciculus hemorrhage had separated both necrotic and regenerating fibers. Some fibers were invaded and surrounded by macrophages and hemorrhage (Fig. 5). All that remained of many muscle fibers were the sarcolemmal sheaths. Many of these were partially collapsed and contained granular clumps of acidophilic material, some of which was present in macrophages (Fig. 6).

The interstitial fibrous connective tissue was increased in amount and was present in the form of broad bands and slender strands, which separated the remaining muscle fibers. The connective tissue was cellular; fibroblast nuclei were increased in number and size. In addition, there were many macrophages, somewhat fewer lymphocytes, a few plasma cells and an occasional neutrophil. Large numbers of well preserved red cells were widely dispersed throughout the damaged parts of the muscle, and many macrophages contained yellow-brown granules of pigment, presumably hemosiderin (Fig. 7). The walls of the small arteries were thickened, and their endothelial cells were unusually large and numerous.

No less striking were the evidences of changes usually interpreted as regeneration of muscle fibers (Fig. 4). In many fibers there was a marked proliferation of the muscle nuclei. Closely packed clusters or rows of nuclei were seen, either just beneath the sarcolemma or in the center of the fiber. As many as fifty could be counted in a short segment of a fiber. Narrow, elongated buds of muscle protoplasm extended out from the muscle fibers exhibiting this nuclear hyperplasia. Some of the thin regenerating fibers were arranged parallel to one another, and others were not oriented in any particular plane. There were well developed transverse and longitudinal striations in some of these fibers.

When the patient was last examined, 5 months after the onset of the illness, bilateral foot drop was still present, and there was moderate atrophy but no tenderness of the anterior tibial muscles. An electromyogram was done by one of us (D. D-B.) at that time. No evidence of electrical activity could be obtained from any part of the tibialis anticus muscle on either side. The natural rhythms of motor activity were present in the peroneal group of muscles on both sides. The tibialis anticus muscle felt unusually firm but was no longer swollen or tender. Passive plantar flexion of the ankle was limited owing to fibrous resistance in the tibialis anticus muscle. Plantar flexion of the great toe on both sides was limited slightly by a similar contracture.

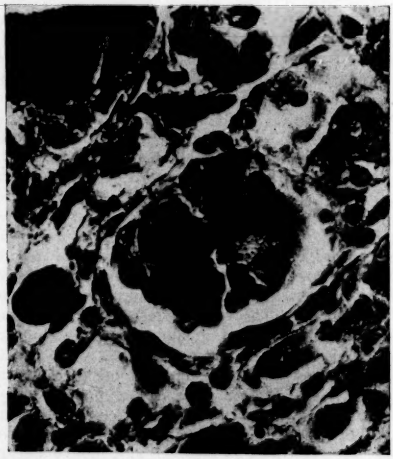

FIGURE 6. *Cross-Section of a Necrotic Muscle Fiber the Remnants of Which are Surrounded by Phagocytic Cells (x 800).*

DISCUSSION

The pain, tenderness, firm swelling and paralysis of the pretibial muscles that constituted the chief symptoms were indicative of a primary disorder of muscles. The absence of reflex changes and sensory loss and the lack of electrical excitability of the involved muscles tended to exclude the possibility of disease of the peripheral nerves. The erythema and warmth of the skin were believed to signify an acute inflammatory reaction in the underlying muscles, — an acute myositis, — and the fever, malaise and albuminuria were regarded as systemic manifestations.

FIGURE 7. *Hemosiderin in Macrophages Appearing as Refractile Granules and Lymphocytes, with the Plasma Cells and Macrophages between Multinucleated Muscle Fibers (x 800).*

There was at first much uncertainty about the type of muscular disease with which we were dealing. Polymyositis, dermatomyositis, trichinosis and acute suppurative myositis were all considered but seemed unlikely because of the acute onset after strenuous exertion, the lack of definite skin lesions and the restriction of the process to the pretibial muscles. Other diseases considered in the differential diagnosis were erythema nodosum, diffuse vascular diseases, such as disseminated lupus erythematosus and periarteritis nodosa, and pretibial fever. Erythema nodosum was ruled out by the absence of definite skin nodules and by the occurrence of pronounced muscle swelling and paralysis, to which we could find no reference in

medical writings. Diffuse vascular diseases could not be established since most of the cardinal criteria of these diseases were lacking. Pretibial fever, in which the leading clinical manifestations have recently been described by Daniels and Grennan,[1] was suggested by the location of the pain, the fever and the systemic symptoms. However, the case reported above deviated widely from published accounts of this disease, in which fever, splenomegaly and skin eruption were prominent features and muscle paralysis did not occur.

The muscle biopsy, though giving only a fragmentary picture of the pathology, was of considerable help in ascertaining the possible causes of this clinical condition. The extensive necrosis of muscle fibers, the hemorrhage, the proliferation of fibrous connective tissue and the muscle regeneration indicated an acute destructive process that was subsiding. The lymphocytes, the occasional neutrophils and eosinophils and the plasma cells were believed to be a reaction of tissue necrosis. These findings corresponded approximately to the microscopical changes described in human beings by Lorenz[2] and others and by Clark[3] in animals several days after experimental crushing of muscle tissue. The histopathology in this case differed from that reported in bacterial and parasitic infections of muscle and from the less well defined dermatomyositis or polymyositis.

The origin of the muscle necrosis could not be established with certainty. Since strenuous exertion — namely, broad jumping on a cement pavement — had initiated the illness, trauma was considered an important factor. Indeed the occurrence of muscle necrosis due to trauma is not without precedent in the medical literature. There is in fact an extensive literature on this subject, which is well summarized by Lorenz[2] and by von Myenburg et al.[4]

However, we have been able to find only 2 cases similar to the one reported above. One was included among a series of cases discussed by Sirbu, Murphy and White.[5] Their patient was a thirty-eight-year-old Filipino soldier who developed severe pain over the anterior aspect of both lower legs after a prolonged march. The anterior tibial muscles of both legs were swollen and tender and at operation bulged through the incised fascia as gray-white masses. Upon release of pressure by removal of a portion of the crural fascia the right leg recovered fairly well, but the muscles of the left were almost completely gangrenous and had to be excised. The subsequent course of this illness is not given. The authors suspected a vascular lesion because of the extent of the necrosis.

The other case was recently presented by Phalen,[6] who reported 4 cases of ischemic necrosis of the anterior crural muscles incident to trauma. Three of his cases were quite different from ours in that a fracture of the tibia and fibula had been attended by necrosis of the pretibial muscles. But in the other case painful swelling and paralysis of the pretibial muscles of one leg had occurred in a young man who had walked a half mile. At operation the muscle tissue was found to be soft, friable and reddish gray. Injury or functional occlusion of the anterior tibial artery was offered as an explanation for the muscle paralysis.

The possible relation of this condition to the mild and relatively common affliction of muscles known as "shin splints" and to traumatic myalgia is interesting. Every athletic coach is well acquainted with the tenderness and pain in the pretibial muscles that occurs when runners, broad jumpers and hikers begin to train. The affected muscles become firm and swollen, and any attempt at active or passive flexion and extension at the ankle is painful. The cause is assumed to be recurrent trauma of the unconditioned muscles; nothing is known of the pathology. Rest and warm applications may be required in severe cases, but most athletes "walk off" their ailment. We have been unable to find any record of paralysis and subsequent atrophy of muscles, and Dr. Christoff* here knew of none. Trauma, which produces acute and chronic myalgia, is also quite common, but again no adequate pathological studies are available and it seems unlikely that it would be attended by complete paralysis.

Rupture of muscles after violent exertion is also well known, occurring not infrequently as an occupational disease. This subject is reviewed in detail by Lorenz.[2] Gilcreest,[7] who has discussed the subject at length, has observed rupture of the neck muscles in loaders and packers, of the biceps and triceps in baseball pitchers and weight lifters, of the adductors of the thigh in horseback riders and of the rectus abdominis in an Indian broad jumper. The usual sequence of events is a violent contraction of a muscle group when the antagonists are suddenly brought into action, a snap, severe pain, swelling and local bulge in the muscle. The rupture, which may become complete only after twenty-four hours, is usually in the belly of the muscle and although the muscle is weakened, paralysis does not occur unless all the tendinous attachments are torn. It is unlikely that muscle rupture can be held responsible for the firm swelling, paralysis, erythema of the skin and fever that occurred in the case reported above.

The only satisfactory explanation of the pathogenesis of this syndrome that we are able to suggest is that violent contraction led to rupture of muscle fibers and possibly to hemorrhage. The affected pretibial muscles, contained as they are in a fairly rigid compartment formed by the tibia, fibula, interosseous membrane and crural fascia, were further damaged by the ischemia incident

*Director, Department of Student Health, Boston University (personal communication).

to edema and hemorrhage. We were unable to obtain evidence, either clinical or pathological, of injury to the anterior tibial artery as proposed by Sirbu and his co-workers[5] and Phalen.[6] However, more complete pathological studies are necessary to settle this point. The possibility that influenza or respiratory infection had predisposed the muscles to trauma can neither be affirmed nor denied though the lack of distinct symptoms preceding the trauma makes this unlikely.

Summary

A case of a young man who developed severe pain, swelling and erythema of the anterior aspects of both legs after broad jumping on a cement pavement is presented. This was followed by paralysis of the pretibial muscles, which subsequently underwent atrophy. A muscle biopsy, performed seventeen days later, revealed extensive destruction of muscle tissue and hemorrhage and slight regenerative activity of some muscle fibers. Trauma was believed to be the main etiologic factor.

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NODULAR GOITER AND THYROID CANCER

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IN THE therapeutic attack on malignant tumors in general, the accumulated experience of generations has established as virtually axiomatic certain well defined principles.

The first is the folly of attempting to arrive at a diagnosis by observation of the continued growth of a tumor or area of nodularity until its malignant nature is clear and unmistakable. As stated by Taylor,[1] one must answer the question, "What is the disease?" It must be answered early, by biopsy or by removal of the lesion in question.

A second is the great utility of the principle of prophylactic removal of lesions that, though apparently benign, are known to be at times actually malignant or to be capable of malignant degeneration. This principle is almost universally accepted in the therapy of such conditions as leukoplakia of the oral cavity, keratosis of the skin, papillomas of the bladder, polyps of the rectum and colon and kraurosis vulvae.

On the basis of this fundamental attitude, supported by an impressive array of statistical evidence indicating a high incidence of cancer in the nontoxic nodular goiter, most surgeons who have concerned themselves with the subject have favored removal of such growths. The incidence of cancer in nontoxic nodular goiter, as reported from representative surgical clinics in different parts of the country, varies from 4.8 to 11.0 per cent (Table 1). All reporting clinics have shown a higher incidence in single adenoma than in the multinodular nontoxic goiter, varying from 9.0 to 24.0 per cent (Table 2).

Table 1. *Incidence of Cancer in Nontoxic Adenomatous Goiters.*

Author	Cases of Goiter	Cases of Cancer	
		No.	Percentage
Hare[2]	5,052	246	4.87
Ward[3]	3,539	168	4.8
Hinton and Lord[4] (toxic and nontoxic)	184	14	7.6
Cole, Slaughter and Rossiter[5]	100	11	11.0
Anglem and Bradford	550	42	7.6

These authors and many others advocate, on the basis of the figures presented, the principle of prophylactic thyroidectomy for nodular goiter, even though it may be symptomless.

Table 2. *Incidence of Cancer in Single Nontoxic Adenomas.*

Author	Cases of Adenoma	Cases of Cancer	
		No.	Percentage
Hare	1971	236	12.0
Cole, Slaughter and Rossiter	92	22	24.0
Anglem and Bradford	363	33	9.0

It is recognized that the incidence of cancer in simple diffuse goiter, in primary hyperplasia and

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in toxic adenomatous goiters is so low as to be of no significance in the general problem. It is also recognized that certain adenomatous goiters require thyroidectomy because of toxicity or because of substernal, retrotracheal or intrathoracic extension productive of serious pressure symptoms. The operation in these cases can in no sense be considered a prophylactic procedure.

The crux of this problem thus revolves about the attitude that should be taken toward the single adenoma and the relatively symptomless and usually small or moderate-sized multinodular nontoxic goiter. The validity of the principle of prophylactic thyroidectomy in such cases has recently been questioned by Rogers, Asper and Williams,[6] who support their point of view by data obtained from the study of the records of 3221 cases drawn from all services of the Boston City Hospital, the Johns Hopkins Hospital and the Massachusetts General Hospital.

TABLE 3. *Incidence of Cancer in Various Types of Goiter.*

TYPE OF GOITER	NO. OF CASES	NO. OF CANCERS	PERCENTAGE
Nontoxic adenomatous	550	42	7.6
Single adenoma	363	33	9.0
(Cancer unsuspected)	(354)	(24)	(6.7)
Multiple adenoma	187	9	4.8
Toxic	811	4	0.49
Toxic adenoma	105	2	1.9
Primary hyperthyroidism	706	2	0.28
Thyroiditis	16	0	0.00
Totals operated	1377	46	
Average			3.3

In support of their point of view, Rogers, Asper and Williams lay great emphasis on an alleged discrepancy between the incidence of thyroid cancer in surgical specimens and that in "clinical" and autopsy material; the significance of the factor of variability is the degree of malignancy in thyroid cancer and in the morbidity and mortality associated with thyroidectomy. VanderLaan[7] also stresses the low incidence of thyroid cancer in autopsy material and implies on the strength of this that surgical pathologists are diagnosing as thyroid cancer lesions that are not malignant.

Since nodular goiter is not uncommon, it is highly desirable to arrive at some measure of accord regarding the therapy, if any, that should be recommended to the patient with an otherwise symptomless uninodular or multinodular goiter.

A challenge such as that implied in the paper of Rogers, Asper and Williams serves a useful purpose in compelling a reappraisal of prevailing attitudes and critical re-examination of the bases on which they rest.

With these considerations in mind, we have undertaken a critical and objective review of the data on which the two conflicting points of view rest and have, in addition, made a study of the records of 1377 patients from the Thyroid Service at the Massachusetts Memorial Hospitals and from our office. All patients having had thyroidectomy or excision of thyroid nodules are included. Patients having had two-stage operations are counted only once. Among the 1377 patients, cancer was encountered in 46 cases, or 3.3 per cent. The incidence of cancer among the various types of goiter is indicated in Table 3.

The types of cancer encountered were as follows: papillary adenocarcinoma (18 cases); adenocarcinoma (11 cases); small-cell carcinoma (5 cases); giant-cell carcinoma (4 cases); Hürthle-cell carcinoma (2 cases); embryonal-cell carcinoma (2 cases); fetal adenoma with blood-vessel invasion (2 cases); fibrosarcoma (1 case); and hemangiosarcoma (1 case). Only 2 cases fell in the borderline group of so-called fetal adenoma with blood-vessel invasion, and in 1 of these the malignant character of the lesion was subsequently confirmed by the development of a metastasis.

Our findings regarding the incidence of cancer fully confirm reports from other surgical clinics in nonendemic areas.

It is our belief that the alleged discrepancy between the incidence of cancer in surgical statistics and that found in "clinical" material does not, in fact, exist. Rogers, Asper and Williams,[6] for example, report an incidence of 1.99 per cent of all patients with goiter, but the total figure on which this calculation is based includes 907 toxic diffuse goiters, 400 nontoxic diffuse goiters, and 377 toxic nodular goiters, all of which play little or no part in this problem. Only 5 of the 74 cases of cancer reported occurred in the toxic group. It is possible from the figures supplied by Rogers, Asper and Williams to calculate the incidence of cancer in the nontoxic nodular group, which, for their entire series, is 4.79 per cent and, for the material that they report from the Johns Hopkins Hospital, 11.2 per cent.

Both VanderLaan[7] and Rogers et al.[6] attach great significance to the infrequency with which carcinoma of the thyroid gland is found as the cause of death in autopsy studies. Jaffé's[8] report of a ratio of 2:1000 is cited by VanderLaan. A ratio of less than 1:1000 in 11,000 autopsies was found at the Massachusetts General Hospital, an incidence of 5 cases in more than 6000 autopsies at the Peter Bent Brigham Hospital, and an incidence of 5 cases in 18,668 cases from the Boston City Hospital. The last figure is so far out of line with the others reported that its accuracy must be questioned.

We believe that this is fallacious reasoning and that the apparent discrepancy is due to the fact that in fatal cases of thyroid cancer the patient has usually had the disease for a long time before the terminal stage is reached and that, except for an

occasional patient who is rushed into the hospital in acute dyspnea and for the rare operative mortality, these patients usually die at home.

In a study of 1657 autopsy records from the Department of Pathology of the Massachusetts Memorial Hospitals for the thirteen-year period from January, 1934 to September, 1947, we found confirmation of the low incidence of cancer as a cause of death in this type of material. Thyroid cancer was not found to be the cause of death in a single case. (657 of these records were on children under the age of ten years). However, neither did we find a single case of cancer of the tongue, floor of the mouth, gingiva, buccal mucosa, or palate, which as a group are considerably more common than thyroid cancer. We also found that our figures suggested that cancer of the duodenum was half as common as cancer of the cervix, — a patent absurdity.

The significant fact we believe to be this: in a period shorter by two years than that covered by the autopsy survey we found 11 patients (from the Massachusetts Memorial Hospitals and from a single private office) who are known to be dead of thyroid cancer. Only 1 of these came to autopsy, and that one at another hospital. It is important to point out that none of the private cases of the remainder of the entire hospital staff are included, and yet their contribution to the autopsy material is included. If a similar situation prevails in other medical centers, and we see no reason to doubt that it does, the actual incidence of death from thyroid cancer is more than ten times greater than autopsy statistics suggest.

Rogers, Asper and Williams[6] emphasize the point that a large percentage of thyroid cancers fall in the group of low or moderate malignancy and suggest that because of this fact a conservative attitude is warranted and that one may wait in dealing with such patients until there is definite objective evidence that cancer is actually present, such as a recent sudden increase in the size of a nodule or the appearance of an increased hardness in the consistence of such a nodule. Against this teaching, it is only necessary to report such end results as those of Ward,[3] who found that when carcinoma of the thyroid gland was diagnosed or suspected on clinical examination, 80 per cent of patients were dead at the end of five years, that when carcinoma was diagnosed at operation, 60 per cent were dead after five years and that when the diagnosis was first made at pathological examination only 20 per cent were dead; it may be pertinent to point out that Cochrane,[9] reporting from the Boston City Hospital on 559 thyroidectomies done between 1925 and 1937, found not a single case of cancer of the thyroid gland diagnosed clinically that was surgically operable.

The mortality and morbidity associated with thyroidectomy is put forward by Rogers, Asper and Williams[6] as a potent argument against prophylactic thyroidectomy. They cite a 15.3 per cent incidence of complications and 5 fatal cases in a series of 431 patients who had thyroidectomies for nontoxic goiter, diffuse or nodular. At least 4 of the operations in the fatal group could by no stretch of the imagination be called "prophylactic."

It is not at all unreasonable to suggest that prophylactic operations performed five, ten, fifteen or twenty years earlier might have obviated these fatal outcomes as well as many of the graver complications. The 15.3 per cent incidence of complications cited is not the incidence of complications that follow thyroidectomy done as a prophylactic procedure, but for the entire group, which unquestionably contained many complicated surgical problems.

It is well known that in the hands of competent thyroid surgeons the incidence of mortality and serious complications is almost wholly limited to the complicated case — the large goiters with retrotracheal, substernal or intrathoracic extension. To cite such complications as an argument against prophylactic removal of discrete adenomas or small nodular goiters is simply to confuse the issue. Lahey[10] has stated:

> The mortality of removal, particularly in the type of adenoma that is likely to become malignant, ought to be zero because it is a discrete adenoma and easily removed. These patients are in the hospital not over a week, so why trade the hazards of malignancy in a thyroid adenoma of this type when there is no risk and the hospital stay is so short?

With this we concur.

In our own series of nontoxic nodular goiters we have excluded all cases in which there was a clear-cut complaint of pressure symptoms, all patients who had substernal, retrotracheal or intrathoracic extension, and all whose goiters were estimated to be 7 cm. in diameter or larger. The remaining group of 331 cases consisted of 220 single adenomas and 111 small or moderate-sized, essentially symptomless multinodular nontoxic goiters. We believe that the term "prophylactic thyroidectomy" can be applied only to this group. Actually, many of these patients wished to be rid of their goiters and the number of cases in which the operation was truly prophylactic was much smaller than the figure given. There were no deaths. The complications occurring in this entire group consisted of: 1 case of deep thrombophlebitis; 2 cases of hypothyroidism; 2 cases of keloidal scars; and 12 cases of serum in the wound, all of which cleared up uneventfully in one month or less.

Conclusions

The high incidence of cancer in single thyroid adenomas from our own study (9.0 per cent) makes obligatory the removal of all single thyroid nodules.

The incidence of cancer in nontoxic multinodular goiters (4.8 per cent) is sufficiently low so that

we concede that the propriety of operating on all such patients might be questioned if there were not other compelling reasons why the growths should be removed. It is our opinion that the multinodular goiter is not a simple benign process, but a progressive disease that goes on, first to develop toxicity in a significant percentage of cases, as indicated by the increasing incidence of toxicity as one ascends the age scale,[11] and secondly, to produce serious mechanical disturbance, chiefly by compression and deviation of the trachea by retrotracheal, substernal and intrathoracic extension. The frequency of such manifestations is indicated by Means's[11] report of an incidence of pressure symptoms in 65 per cent of cases of nontoxic nodular goiter at the Massachusetts General Hospital.

The mortality from operations that can be classed as prophylactic is virtually zero.

The incidence of complications in operations on this class of patient is insignificant, compared with the hazards of leaving the goiter.

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PENICILLIN IN THE TREATMENT OF DIPHTHERIA AND THE DIPHTHERIA CARRIER STATE

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THE importance of diphtheria has been re-emphasized lately by experiences with the disease in foreign countries during the war and its aftermath and by slight but statistically significant increases in the prevalence of diphtheria in this country. The clinical manifestations and complications have been completely described in the older literature. An important aspect of the problem now being developed is the application of antibiotics in treatment. The value of penicillin in diphtheria has been established in extensive clinical trials by Karelitz et al.[1] and by Weinstein.[2] The following investigations confirm their findings in a series of 97 additional penicillin-treated cases and present some clinical evidence bearing on the mode of action of this antibiotic.

Material

The material reported below consists of all patients admitted for diphtheria or the diphtheria carrier state to the 279th United States Army Station Hospital in Berlin, Germany, from July 1 to December 31, 1946. During the period of study diphtheria was constantly at epidemic levels, the troop rate being about 36:10,000 per annum, compared with the over-all rate for the city of 47:10,000 per annum. Cases in which the animal virulence test of the organism cast doubt on the original diagnosis have been eliminated from the study.

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For comparison, an analysis was made of 50 consecutive cases of pharyngeal diphtheria admitted in the six months just prior to the study period and to the routine use of penicillin.

The average length of hospitalization of the non-penicillin-treated patients was fifty-seven days. Whereas all patients were hospitalized for a minimum of six weeks after onset, it is seen that 18 per cent of this series were held for a longer period because of minor cardioneurologic complications, and an additional 6 per cent were held for evacuation to the United States for more serious complications. There were 3 deaths in the series, giving a 6 per cent mortality. Omitting the above three categories, the average length of hospitalization of remaining patients rises to sixty-one days. The reason for this prolonged period of hospitalization becomes apparent when one notes that 57 per cent of the patients had to be held beyond the minimum six weeks merely because they continued to harbor virulent organisms in the nasopharynx. Such prolonged hospitalization of asymptomatic carriers represents a tremendous waste of hospital space and manpower.

Pilot Study

The routine use of penicillin in diphtheria treatment was based upon the results of a study of its effect upon 20 carriers selected on the following criteria: the patients were all asymptomatic convalescents so far as manifestations of acute diphtheria

were concerned; all had been hospitalized for six weeks or more since clinical onset; and from all, triweekly nasopharyngeal cultures were consistently positive for virulent diphtheria bacilli. During the study patients were isolated from new diphtheria contacts, usually 2 patients to a room, both receiving the same type of treatment.

Five cases were treated locally with sprays of a penicillin solution containing 500 units per cubic centimeter, applied to the nasopharynx every three hours day and night for ten days.

Seven cases were treated with 1,000,000 units of penicillin intramuscularly, the dosage schedule being 40,000 units every three hours for twenty-five doses.

Eight cases were treated parenterally with the same total amount of penicillin but given in doses of 20,000 units every three hours for fifty injections.

Cultures were taken three times a week during treatment. The carrier state was considered terminated if, at the completion of treatment, three consecutive cultures at forty-eight-hour intervals and a fourth culture one week later were negative.

TABLE 1. *Results of Treatment in 20 Carriers Hospitalized for Six Weeks or More after Onset with Positive Cultures but No Symptoms.*

TREATMENT	NO. OF CASES	PATIENTS WITH NEGATIVE CULTURES
		%
Local nose and throat sprays of penicillin (500 units per cubic centimeter every 3 hours)	5	20
Parenteral administration of penicillin (40,000 units every 3 hours for 25 doses)	7	28
Parenteral administration of penicillin (20,000 units every 3 hours for 50 doses)	8	87

Local treatment was followed by termination of the carrier state in only 1 patient. Although negative cultures were obtained during and for several days after the short course of parenteral therapy only 28 per cent of the series satisfied the criteria for termination of the carrier state. Excellent results, however, were obtained from the use of the same total dose given in smaller amounts over a longer period, only 1 patient failing to fulfill the criteria for permanent termination of the carrier state (Table 1). The necessity for the four-culture test for termination of the carrier state was demonstrated both in this pilot study and in the material to follow. In many cases the first culture or even the first three failed to show the organisms after penicillin treatment, though later cultures again revealed virulent diphtheria bacilli. On the other hand, no patient who had had the requisite four consecutive negative cultures showed virulent organisms when cultures were obtained on subsequent occasions.

PROCEDURE BASED ON RESULTS OF PILOT STUDY

The results of the preliminary study were promising enough to warrant trial on a larger scale. In addition, it was presupposed that the value of penicillin was not limited to the treatment of carriers but that in acute cases its use might well be expected to reduce appreciably the number of patients continuing to carry virulent organisms for more than six weeks after clinical onset of the disease. Thus, penicillin was incorporated into the routine treatment of both carriers and acute cases.

Patients suspected of having acute pharyngeal diphtheria were immediately given a single average dose of 60,000 units of diphtheria antitoxin and in addition were started on three hourly doses of 20,000 units of penicillin (40,000 units in more severe cases). Penicillin was continued for seven days (fifty doses) or longer if the pharyngeal mucosa was not yet entirely healed.

Carriers were treated initially with the fifty-dose schedule. Only those who failed to respond to this routine were subjected to tonsillectomy. If cultures were still positive after penicillin and tonsillectomy a second identical course of penicillin was given.

PENICILLIN TREATMENT IN ACUTE CASES

Forty-five cases of acute diphtheria were treated with penicillin during the six-month period of study. In comparison with the 50 previous cases, the average length of hospitalization was cut from fifty-seven to forty-five days. Two patients (4.4 per cent) developed serious cardioneurologic complications and were returned to hospitals in the United States. One patient (2.2 per cent) was held beyond the six weeks' minimum for minor cardioneurologic complications. There were no deaths. The average period of hospitalization, omitting the above three categories, dropped from sixty-one to forty-three and one-eighth days. Only three patients were held beyond the six weeks' minimum because of positive cultures, a reduction from 57 to approximately 9 per cent.

TABLE 2. *Results of Treatment in 45 Cases.**

TREATMENT	NO. OF CASES	NEGATIVE CULTURES AFTER TREATMENT	
		NO.	PERCENTAGE
Penicillin alone (20,000 units every 3 hours) ..	45	40	80
Penicillin and tonsillectomy	5	4	80
Penicillin — tonsillectomy — penicillin	1	1	100

*The average contagious period was 26.3 days from the time of admission to the fourth negative culture.

Table 2 shows a further analysis, including a summary of methods of treatment. The average "contagious" period — that is, from admission to the time of receipt of the fourth negative culture after

treatment — was twenty-six and one-eighth days. All the 45 patients received an initial course of penicillin, usually consisting of fifty doses of 20,000 units each; however, a larger dose was sometimes given for the first three days. Forty patients, or 80 per cent, consistently showed negative cultures after treatment. Five patients regarded as penicillin failures, who still showed positive nasopharyngeal cultures at the end of six weeks, underwent tonsillectomy. Thereafter all but 1 showed negative cultures. This last patient was subjected to a second course of penicillin, 20,000 units every three hours for fifty doses, as a result of which there was a prompt termination of the carrier state.

Penicillin Treatment in the Carrier State

During the period of study 52 chronic carriers of virulent *Corynebacterium diphtheriae* were treated. The average period of hospitalization following treatment was sixteen and a half days (Table 3).

Table 3. *Results of Treatment in 52 Carriers.**

Treatment	No. of Cases	Negative Culture after Treatment	
		No.	Per-centage
Penicillin alone (20,000 units every 3 hours for 50 doses)	44	37	87
Penicillin and tonsillectomy	13	12	92
Penicillin (2 courses)	1	1	100
Penicillin — tonsillectomy — penicillin	1	1	100

*The average period of hospitalization after definitive treatment was 16.5 days.

Forty-four patients received an initial course of penicillin, consisting of 20,000 units every three hours for fifty doses. The carrier state was terminated in 37 cases, or 87 per cent. Six of these "penicillin failures" and 7 previously untreated cases were subjected to tonsillectomy, only 1 patient remaining a carrier after this procedure. One patient who failed to respond to the initial course of penicillin was desirous of undergoing a second treatment before submitting to tonsillectomy. This second course was given in the same manner as the first and resulted in cure. Finally, the patient who failed to respond to the initial tonsillectomy later underwent a course of penicillin. This resulted in clearing of a coexistent sinusitis and adenoid hypertrophy and was followed by four consecutive negative cultures at the prescribed intervals.

Discussion

The results of the studies outlined above give further evidence of the value of penicillin as an adjunct in the treatment of diphtheria and the diphtheria carrier state. The present findings are in close agreement with those of Karelitz[1] and Weinstein.[2]

Tonsillectomy has long been recognized as the single most effective procedure in terminating the diphtheria carrier state. Adenoidectomy, the clearing of chronically infected accessory nasal sinuses, corrections of obstructive nasal septal deviation, dental surgery to eliminate foci of infection in the mouth and removal of foreign bodies occasionally found in the nasal passages of children are also well recognized surgical methods of importance in ridding the patient of organisms still obtainable on culture six weeks or more after the clinical onset of acute symptoms.

In general, modern antibiotics are obviating the necessity for much of the surgery of the presulfonamide days in diseases of bacteriologic etiology. This is true of diphtheria. The diphtheria bacillus is relatively resistant to penicillin[3] and quite resistant to sulfonamides.[4] Though it is sensitive to streptomycin,[5] there has been as yet no report of the clinical use of that drug. In the Schick-negative patient the bacillus is characteristically a surface-growing, noninvasive organism depending in large measure on devitalized organic detritus produced by the action of other bacteria to maintain its foothold in the human organism.[6] The surgical measures in common usage in diphtheria are effective because they mechanically eliminate such devitalized tissue. The rationale for the use of penicillin is based as much on its elimination of this detritus as on its specific effectiveness against the diphtheria organism. Here, in contrast to surgery, the site of action of penicillin is the varied organisms giving rise to hypertrophic and devitalized tissue. Three observations support the contention that this is an important factor in the effectiveness of penicillin. A certain class of carriers with necrotic, chronically infected tonsils that do not shrink in size with prolonged use of the antibiotic may confidently be expected to remain carriers until surgery is effected. Secondly, there is a class of patients with acute diphtheria in whom healing of the pharyngeal mucosa is still incomplete at the end of a week of treatment. If penicillin is discontinued according to rigid schedule after seven days (fifty doses), a high percentage of this group of patients will become chronic carriers. If, on the other hand, penicillin is continued a day or two longer until the pharyngeal tissues are re-epithelialized, almost none of the patients will subsequently show positive cultures. Thirdly, large doses of penicillin given over a short period are far less effective than small doses totaling the same amount but given over a longer period in shrinking and returning infected, hyperplastic pharyngeal lymphoid tissue to a healthy state. Corresponding with this is the superior effectiveness of small, longer continued penicillin doses in ending the diphtheria carrier state.

The present study does not suggest that penicillin supplant antitoxin in the treatment of acute diphtheria or replace surgery in the treatment of

the carrier. It indicates that penicillin is a valuable adjunct to antitoxin that should continue to be recognized as the specific form of treatment. Moreover, penicillin decreases the number of cases in which surgery is indicated, but does not lessen the necessity for operation in a selected group of patients.

Summary

An attempt to demonstrate the value of penicillin as an adjuvant to the treatment of diphtheria and the diphtheria carrier state is made through the presentation of the results of its use in 45 cases of acute diphtheria and 52 cases of carriers of virulent diphtheria organisms. For comparison these results are reported along with those obtained in treating 50 patients during the same epidemic but in the six previous months when penicillin was not used as part of the routine treatment.

The probable mode of action of penicillin is discussed.

It is concluded that penicillin is a valuable adjunct in the treatment of diphtheria and the diphtheria carrier state but that it does not supplant the use of antitoxin in the acute stage or obviate the necessity for surgery in a selected group of carriers.

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SURGERY OF ELEPHANTIASIS OF THE SCROTUM OF FILARIAL ORIGIN*

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A NEW interest in tropical diseases has been attained in American medicine because of the widespread contact with exotic diseases by troops in the worldwide conflict that terminated on V-J Day. Among these none is more bizarre than elephantiasis of *Filaria* (*Wuchereria*) *bancrofti* origin. This report deals with experience gained with this affliction among natives of Polynesian extraction in the Society Islands in French Oceania. I obtained the material for this paper in my capacity of chief of the Surgical Service of the 8th Station Hospital under the command of Lieutenant Colonel Julius Sobin, who performed the major part of the actual surgery and whose skill contributed in a large measure to the success of the enterprise.

The patients were studied for a period of twenty-six months on one of the Society Islands occupied by United States forces. Although inter-island traffic was limited to a degree by war conditions, blood tests were performed on hundreds of natives, revealing an incidence of microfilariae in some localities as high as 70 per cent. This incidence is about as high as that found anywhere in the world. De Rivas[1] states:

> In Polynesia, the micro-filariae show no periodicity and are present in the blood in about equal numbers both day and night. In other areas they show a nocturnal periodicity, it being definitely established that they are much more numerous in the peripheral blood at night than during the day.

General Description

In filariasis associated with *W. bancrofti*, the adult parasites usually live in the lymph nodes and lymphatic vessels, and in connective tissues. After pairing, the females emit numbers of microfilariae, which reach the blood stream via the thoracic duct and by penetrating the thick walls of the lymphatic vessels into neighboring capillaries. The infection is transmitted from man to man by means of a mosquito, the species varying according to locality. In Polynesia two species, *Aedes variegatus* and *Culex fatigans*, are responsible. When the insect has sucked blood from a person harboring microfilariae, the parasites migrate to the insect's thorax and there undergo considerable development. In fifteen to twenty-one days the microfilariae become mature larvae and migrate to the head and then to the proboscis of the insect. If the mosquito sucks blood at this time, the parasites are able to find their way to the skin of the host and to penetrate it — independently of the wound made by the insect. The larvae, by an unknown process, reach sexual maturity when they find their permanent abode in the lymphatic vessels and lymph nodes within the host. They become adult worms and in a fresh state are

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yellowish white and transparent, resembling thin catgut. They frequently coil together, ten or a dozen being found in a single lymph node. The male is 4 to 4.5 cm. long and 0.1 mm. in diameter, whereas the female is twice as long and thick. The microfilariae are the product of conception of paired adult worms and are found in peripheral blood. Seen in a fresh smear, the microfilariae appear to be snakelike and exhibit twisting and lashing movements, but they do not progress, either laterally or longitudinally.

Pathology

The disease evoked by infestation of lymphatic vessels by adult worms is at first a state of lymphangitis with all the signs of acute inflammatory reaction. Very frequently secondary invaders, notably streptococci, cause abscess formation. After a few attacks there is a tendency to fibrosis and considerable hypertrophy of the lymphatic vessels. New and irregular formation of lymphoid tissue surrounded by fat succeeds each attack. An elephantoid process forms by repeated attacks, with predilection for the breast in the female and the scrotum in the male. A typical case of scrotal elephantiasis is illustrated in Figure 1. It is my opinion that these organs favor elephantoid development because of their more dependent lymphatic circulation, which in turn encourages the mechanical obstruction that is always the cause of elephantiasis.

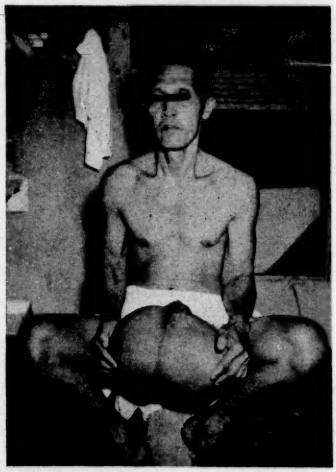

Figure 1. *Elephantiasis of the Scrotum in a Polynesian Native.*

Clinical Manifestations

Many people infected with filariasis suffer no inconvenience whatever. Thousands of troops stationed in the Pacific became infested with *W. bancrofti*. Between 1942 and 1945 in all theaters of war Sapero[2] estimated that 14,000 members of the armed forces contracted filariasis. Predominantly, the infestation was acquired in the Pacific Theater. Had it not been for the marvelous efficiency of service troops in mosquito-control units, there would undeniably have been a much higher incidence of occurrence than that reported. These units operated in areas of malaria, filariasis and other tropical diseases with great efficiency, mainly by ditching, draining, spraying with DDT and other insecticides, screening and by education of both troops and natives in methods of mosquito control. The troops that became afflicted by repeated bites from infected mosquitoes exhibited early signs of the disease, usually either an acute funiculitis or epididymitis or a superficial lymphadenitis.

When the patient was transferred to a nonfilarial area, the entire symptomatology faded away, and follow-up study in all these cases has shown an almost universal recovery, with practically no recurrence.

On the other hand by repeated attacks about 50 per cent of the natives had a large variety of symptoms, and 5 per cent had elephantiasis. The more usual conditions were lymphangitis and adenitis; elephantoid fever and elephantiasis; abscess; inflammation of the spermatic cord and epididymis; hydrocele; cystic enlargements of the skin, lymph nodes and breasts; fistula; chyluria and chylous conditions of the peritoneum and intestine; and chylocele synovitis.

Diagnosis

The recovery of living or dead calcified parasites in a lymph node or abscess and the occurrence of microfilariae in the blood constitute positive diagnostic data. However, the microfilariae frequently disappear from the blood after elephantiasis has occurred, owing to death of the parent parasites within the body of the host. Matas[3] states that recurrent erysipelatous inflammation with progressive hypertrophy is diagnostic.

Blood studies may be of value. The presence of eosinophilia in the absence of intestinal helminthiasis is suggestive. At the height of the attack the eosinophil count may rise to 25 or 30 per cent. Recently, O'Connor[4] has used x-ray examination to demonstrate the presence of calcified worms, a new aid in diagnosis.

Surgery of Scrotal Elephantiasis

There is little in the American medical literature denoting the technic of surgery on the patient with scrotal elephantiasis, because of an almost total lack

of patients with this affliction within the continental limits of the United States. French and South American surgeons have had great opportunity to pioneer in this field and have published reports of successful surgery performed in scattered areas of the globe. Since the pathologic findings vary materially in different locations, the surgeon, perforce, must adapt his technic to suit the conditions. There is no one type of operative procedure that will answer all the needs as found in various locations. A search of the literature discloses exactly the same number of technical approaches as the number of writers. Certain basic features however are constant findings in these reports:

Infection is always present, and precautionary measures must be adopted. Bankoff[5] states that 95 per cent of the cases will suppurate, adding: "The complication can be eliminated today by packing sulfonamide powder directly into the wound."

Preservation of the penis and testes is vital. In some locations scrotal elephantiasis is always accompanied by hydrocele, which must be handled with the established surgical procedure of excision.

Hemostasis and control of bleeding are axiomatic. de Savitsch[6] points out the universal need of applying a tourniquet at the base of the scrotum and doubly ligating the large blood vessels found medial to the cord to avoid the serious consequence of hemorrhage.

In this series of 24 cases the scrotum was universally affected on both sides, with concomitant bilateral hydrocele. The hydroceles were usually disportionate in size, giving the appearance of more scrotal involvement on the side of the larger hydrocele. Since many patients had skin manifestations of yaws as well as filariasis, they were given three intravenous treatments of arsphenamine before hospitalization. This always sufficed to eradicate yaws as a possible contaminating agent.

The average age was thirty-eight years. The scrotal elephantiasis had been present for an average of eight years, and the scrotal redundancy averaged 15 pounds, which does not include the fluid contained within the hydroceles.

Sexual intercourse was impossible for the patients prior to operation because the penis was deeply imbedded within the tumor mass. These people were Polynesians, and whereas this paper is not intended to deal with ethnology, it should be remarked that the male Tahitian is brown-skinned, extremely muscular and well nourished and, despite his filarial infestation, a very healthy being. Under these conditions it was not necessary to build up the patient prior to surgery by the use of hematinics, vitamins, amino acids or chemotherapy. It was enough to rid him of yaws and to sterilize the skin locally.

Under ether anesthesia the patient received his final skin preparation, and an elastic tourniquet was placed tightly around the scrotum and as near the perineum as possible. The penis was located by palpation and held away by the assistant's right hand. The surgeon then located the testicle on one side and exposed it by a lateral incision. The hydrocele, which was always present, was corrected by an inversion procedure. The same surgery was repeated on the other side. It was not necessary to provide a pulley attached to the ceiling to elevate the tumor mass, as reported by de Savitsch.[6] The large blood vessels were isolated, doubly ligated and divided as high as possible.

In the next step the two lateral incisions were extended on each side of the mass in a curvilinear direction, meeting in the midline posteriorly. Anteriorly, the lateral incisions were joined by a long straight flap, which provided skin for a new sheath for the penis in the event that it was found necessary to sacrifice the integument of the old sheath. However, the sheath in each case was found to be resilient — in fact, quite normal — and to have no relation to the extremely fibrotic and thickened skin of the scrotum. The main tumor mass was then amputated distal to the lines of the incisions, and all bleeding vessels were carefully ligated after removal of the elastic tourniquet.

In reports from other localities — notably, the French Congo — the surgeons had to borrow skin from normal sites to provide new sheath and the new scrotum, but in the present report this was not necessary owing to the integrity of the old sheath and to undermining of the skin of the remaining scrotal flaps. The wound was dusted with sulfonamide powder and closed lightly with nonabsorbable suture material. A rubber dam was inserted in the most dependent part of the wound, and a thick gauze was secured by a T binder. Postoperatively the wounds healed rapidly and with only moderate infection. Usually in ten days the patient was discharged from the hospital to resume his usual haunts, unencumbered by his previous disability and once again able to cope with economic and social obligations.

Military horizons were extended. The Army moved on to new shores, and the results could not be observed over a sufficient period for a report on long-term postoperative findings. It was obvious, however, that psychologically the patients were extremely benefited. There were no indications of impending recurrence of elephantiasis in any case.

Summary

A description of elephantiasis of the scrotum of filarial origin among natives in Polynesia is presented. The mosquito vectors are named, and a general picture of the resulting pathology is described.

It is pointed out that veterans who had contracted the infestation during wartime have made virtually 100 per cent recoveries after their return to nonfilarial areas.

Drug treatment of filariasis has been attempted with no great success throughout the regions where it occurs. Surgery offers the only benefit to those who have acquired elephantiasis as a result of many repeated bites of infected mosquitoes.

The technic of a surgical approach to the problem of elephantiasis of the scrotum is presented.

50 Main Street

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MEDICAL PROGRESS

CHEMOTHERAPY OF NEOPLASTIC DISEASE

I. Methods of Approach

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IN RECENT years there has been a remarkable increase in research directed toward the discovery of chemical substances of therapeutic value in neoplastic disease. This endeavor has been stimulated by many factors: the intensification of medical research in general and cancer research in particular; the notable examples set by the development of antibiotics for bacterial infections; public demand for effective methods of controlling the disease; and the ever-present, suffering, doomed, but often lingering, patient with cancer. Recent chemotherapeutic advances — estrogens in prostatic carcinoma, nitrogen mustards in the lymphomas and urethane in the leukemias — have provided some encouragement toward the solution of a problem that has been viewed with unrelieved pessimism by many experienced investigators.[1]

One of the chief objectives of cancer research is the development of effective therapy. With the belief that methods of treatment will follow from an understanding of the disease itself, many investigators concentrate their efforts on the biologic and chemical aspects of cancer. Others, with more faith and often less method, are directly concerned with the therapeutic problem. Investigations in cancer chemotherapy are in progress at the National Cancer Institute[2] and at a number of universities and hospitals. Many projects of this type are sponsored by the American Cancer Society on recommendation of the Chemotherapy Section of the Committee on Growth of the National Research Council.[3] Some pharmaceutical companies, which routinely test new chemicals against a variety of infectious organisms and in various biochemical systems, now include in these tests the neoplastic cell. In short, a great and direct effort on the problem of cancer chemotherapy is underway. This is evidenced by the numerous reviews that have appeared on the subject since 1945.[4–12]

It seems appropriate to review the basic ideas, the laboratory technics and the methods of clinical evaluation established in the cancer-chemotherapy program, and to discuss the status of the agents that have been proposed, utilized or publicized as having a role in the treatment or management of cancer in man. At present the problem has attracted the attention of most of the scientific disciplines and of many clinical investigators. The modern approach is still in its formative phase, and there is a great deal of room for controversy and differing opinions.

It is hoped that this brief review will help to clarify the several aspects of the complex field of cancer chemotherapy, and substitute concrete expression for what often seems to be wishful thinking.

Approaches to the Problem

It may be assumed that, if the proper approach were known, the attempt to discover curative drugs for cancer would be immensely simplified. Since, unfortunately, there are many conceptions of the chemotherapy problem, none of which is generally acceptable and all of which may be untrue, the

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direction of research must be based on theory rather than fact. As an example of this, some representative attitudes on cancer chemotherapy have been culled from the recent literature.

Woglom[1] has summarized, in a rather caustic fashion, the efforts to treat cancer by means of tumor extracts or autolysates, organ extracts, enzymes, metals, agents interfering with aerobic glycolysis, fever, cold, dyes, snake venoms, vitamins, various chemicals and a number of miscellaneous substances. His review indicates that many thousands of remedies have been tried in the treatment of cancer, that reports of favorable results usually originate from quacks or deluded or ignorant men and that the possibility of finding a cure for cancer is next to impossible.

Haddow[4] has set down more explicitly the difficulties of discovering a specific therapeutic agent against cancer:

> It has always been a matter for legitimate doubt whether a therapeutic agent could impair the growth of malignant cells, without equally damaging the normal cells and especially those which are engaged in active division, for example, in the intestinal mucosa, the bone marrow, and the generative organs. An even more serious obstacle is the fact that the malignant variant is to all intents and purposes quite permanent and irreversible. Hence, even if its growth is impeded by any agent save the most specific (so far unknown), it is likely after a longer or shorter interval, to recover and recur . . . there can be no misunderstanding as to the almost insuperable problem which the chemotherapy of cancer presents, and which, in search of a comparison, we can almost liken to a biological counterpart of the squaring of the circle. It is indeed true that those who have considered the matter most thoroughly are under the least illusion as to its practicability.

In spite of these real impediments, Haddow has formulated his attack on the problem as follows: ". . . the best prospects of success . . . should come from persistent investigation of the mode of action of carcinogens, so that by increasingly exact and quantitative knowledge of the process as it occurs in one direction, we may estimate at any rate the feasibility of its deliberate reversal."

Burk,[13] on a premise elaborated in a recent book by Greenstein,[14] writes more optimistically:

> The hope for the (chemical) approach lies mainly in the finding of modern biochemistry that whereas etiologically and morphologically cancer represents a great group of diseases, biochemically it presents a surprisingly uniform metabolic, chemical pattern that is characteristic, and therefore potentially subject to a unique or reasonably small number of chemotherapeutic agents, just as large classes of pathogenic microorganisms now are. The established biochemical "much of a muchness" of cancers may be regarded as a by-pass to an otherwise seemingly endless complexity of the problem.

Algire[15] has stated the belief that a common factor in the neoplastic process is the stimulation to the formation of new capillaries:

> It should be emphasized that an outstanding characteristic of the rapidly growing tumor is its capacity continuously to elicit the production of new capillary endothelium from the host. This characteristic of the tumor cell might possibly be the real underlying factor responsible for the autonomous growth inherent within the tumor cell; and from the standpoint of the host this capacity would seem to be a critical if not the critical expression of the neoplastic change. Since in tumor regression this ability to elicit a continuing vascular proliferation is lost, from the broad viewpoint of tumor therapy the study of the mechanism of this continuous vascular proliferation presents a major problem in cancer research.

On this basis, it appears that a study of agents interfering with capillary proliferation might furnish a generally useful chemotherapeutic agent against cancer.

The virus theory of cancer has been most persuasively presented by Oberling.[16] In this theory, however, the ubiquitous, tissue-specific viruses are presumably numerous and different so that it is difficult to imagine a common chemotherapeutic agent acting on all of them. If one can accept the virus hypothesis, it does not seem much more

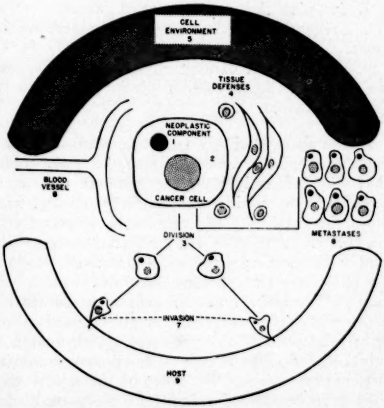

FIGURE 1. *Diagram of the Possible Points of Attack by Chemotherapeutic Agents on Cancer and Its Manifestations (Reproduced from Karnofsky[12] by Permission of the Publishers).*

difficult to conceive of a single agent or series of agents interfering with the proliferation or activity of these viruses.

Using the broad definition that "cancer chemotherapy is the use of any chemical substance administered systemically which, while relatively nontoxic to the host, will interfere with, favorably modify, or destroy a neoplastic growth or alleviate its deleterious effects on the host," Karnofsky[12] has discussed the various possible avenues of chemotherapeutic attack on cancer; these are shown in Figure 1, with examples from agents under current study. The possible effects are as follows:

1. On the neoplastic component of the cell, which may be a single substance or a physiologic process occurring primarily anywhere in the cell.

2. On the normal cell, which is the portion of the neoplastic cell that retains the functional and chemical characteristics of normal tissues and the tissue of origin — for example, nitrogen mustards, urethane and radioactive iodine.

3. On the dividing cell, mitosis being essential for the manifestations of the neoplastic process — for example, colchicine.

4. On the tissue defenses, suggesting that in some cases the tissues develop a defensive reaction against cancer.

5. On the cell environment, on the basis that the growth of certain normal tissues depends on the presence of specific substances in their environment — for example, estrogens.

6. On damage to the blood supply, on the basis that cancer tissue requires a good blood supply for growth — for example, Shear's polysaccharide.

7. Stopping the invasiveness of cancer.

8. Preventing the development of cancer metastases.

9. Protecting or strengthening the host against the systemic derangements produced by certain types of tumors.

In the absence of any known method of attacking the neoplastic process directly, any substance that may indirectly injure or influence the cancer cell should be considered suitable for clinical trial. Since the possibility of achieving a universal cancer cure seems to lie in the far distant future, "the cancer chemotherapist has progressively lowered his objectives from finding substances which will cure only certain types of cancer, to substances which will control cancer or certain types of cancer or certain manifestations of cancer, and, finally, to substances that have only a temporary palliative effect on the disease."[12] Most of the agents that have been considered suitable for inclusion in this review belong to the last group.

Laboratory Technics

Special laboratory technics, involving the use of neoplastic cells and tissues, have been developed to test substances in a preliminary and general fashion for any selective activity against cancer (screening methods), to examine the mechanisms whereby certain substances affect the growth of tumors and to compare quantitatively the chemotherapeutic activity of different members of a given group of substances. In principle, these methods have much in common with those used in bacterial chemotherapy. However, they are more complicated and require more time than antibacterial methods, the results are less reproducible, and the data obtained are, consequently, more difficult to analyze. Furthermore, the validity of conclusions drawn from these data, in terms of the efficiency of an agent in affecting neoplastic as compared with normal cells, is often open to question. Because these methods are in current use[17] and represent an important part of any chemotherapeutic program, it is necessary to review them briefly.

The tumor-bearing mouse is the most commonly used tool in cancer chemotherapeutics; the rat, rabbit and chicken are employed to a lesser extent. Mice can be inbred with relative ease to the point of being homozygous, and strains of mice have been inbred for selected characteristics such as a high incidence of spontaneous leukemia and mammary carcinoma. Tumors of certain types may also be regularly induced by carcinogenic compounds. Within appropriate strains of mice, tumors may be easily and consistently transplanted, and a host of different transplantable tumors are available.

This variability of material and also of testing procedure must be carefully considered in any chemotherapeutic screening program. For example, the sex, strain, degree of inbreeding or homogeneity, age and nutritional and reproductive status of mice may vary. Tumors may be spontaneous, carcinogen induced or transplanted, and they may differ in their site of origin, histologic structure, rate of growth, ability to metastasize, sensitivity to various procedures and ability to grow in heterozygous mice. In the performance of a chemotherapeutic experiment on tumor-bearing mice, the test substance may be given orally, subcutaneously, intraperitoneally or intravenously; it may be given in the maximum tolerated dose, or at a fraction of this dose, or administered as a single dose, or given repeatedly over a period, and it may be administered in combination with other agents. Therapy may be started when the tumor is transplanted or when it is first palpable, or when it reaches a certain size, or a certain number of days after transplantation. In examination of the mouse for evidence of chemotherapeutic effect, tumor injury may be measured by evidence of histologic damage, by change in the size of the tumor or by the survival time of the tumor-bearing mouse.

In vitro tests, egg culture and tissue culture are additional methods currently in use. Thus, an almost infinite variety of chemotherapeutic experiments is possible. Since it is not "logistically" feasible to run all possible variations of these methods for each compound, it is conceivable that the activity of a highly specific drug, effective against a certain tumor in a certain strain of mouse under certain conditions of administration, would be missed in arbitrarily selected procedures. It is more reasonable to assume, however, that a therapeutically active substance will have a broad range of activity, even though its effectiveness within this range may vary considerably. On the latter basis a number of arbitrarily designed testing technics

are being used, and some of these are briefly described below.

The most common methods involve the use of *transplantable solid tumors* in mice or rats.

The National Cancer Institute uses the Sarcoma 37, inoculated intramuscularly into the flank of the mouse. The chemotherapy screening technic is described as follows[18]:

> Injection into mice, bearing a 1-week-old implantation of Sarcoma 37, of a single, maximum tolerated dose. The injection is made into the flank opposite the side bearing the tumor. Sacrifice of the mice at 8, 20, and 48 hours after the injection. Recording of the gross autopsy findings. Fixing of tumor tissue in Zenker-acetic and in acetic-orcein. The wall of the small intestine is taken as control tissue. Evaluation of the cellular changes produced by the treatment.

This test may disclose substances injurious to rapidly dividing cells or to newly formed capillaries, and it may possibly disclose an agent selectively injurious to tumor cells.

A somewhat similar method is described by Laszlo and Leuchtenberger.[19] A transplantable tumor, the Sarcoma 180, is inoculated subcutaneously in mice. One week later, when the tumor is definitely palpable, the test material is injected twice daily for two days, and then the tumors are removed and weighed, and the weights compared with appropriate controls.

In another type of experiment, a tumor is transplanted subcutaneously and observed for an arbitrary period, or until growth is well established. Treatment may then be instituted in several ways: the agent may be given by mouth[20] or by parenteral injections.[21] The mice may be observed for a standard period, and the size of the treated tumors compared with the controls, or observed indefinitely until the tumor kills the animal or until complete tumor regression occurs. The size of the tumor at death, the incidence of tumor regression or the survival time of the tumor-bearing mice may be used as criteria of effect. The weights of the mice must be observed during therapy, since starvation[22] or nonspecific intoxication may influence tumor growth.[23]

Recently, *transmitted leukemia* has come into more prominent experimental use.[24–26] Susceptible mice are inoculated intraperitoneally or intravenously with a suspension of leukemic cells. Therapy is begun shortly afterward, and is usually continued at the maximum tolerated dose for several weeks. The survival time of the treated as compared with the untreated mice is used as an index of the therapeutic efficacy of the test agent. This procedure will disclose drugs that inhibit rapidly growing cells or selectively inhibit neoplastic cells. It is possible, however, that some drugs increase survival time indirectly by supporting the mice against the systemic consequences of leukemia without acting directly on the neoplastic cells.

Transplanted tumors or leukemia are most practical for the screening of chemotherapeutic agents. In animals bearing transplanted tumors, however, the host-tumor relation usually must be considered abnormal, and a more critical evaluation of chemotherapeutic activity may be conducted in mice with *spontaneous* or *carcinogen-induced* tumors. Suitable groups of these mice are often difficult to obtain. It must also be realized that each spontaneous tumor has its own characteristic properties and rate of growth; survival time and tumor regression studies must therefore be carried out on larger numbers of mice than are necessary with the standardized method in which the disease is transmitted. Usually, if an agent is effective against transplanted tumors, confirmatory tests are run on spontaneous or carcinogen-induced tumors.

A *cytocidal technic* for determining the dosage of a chemical necessary to inactivate tumor cells in vivo has been described by Burchenal.[27] This method is applicable to drugs that do not kill the test animal immediately, even when given at several multiples of the LD_{50}.* Mice with established transmitted leukemia are injected with various multiples of the LD_{50} of the test substance. At an arbitrary period after injection, or just before death, the animal is sacrificed and a suspension of its leukemic cells (usually a splenic suspension) is injected into susceptible mice to determine their viability. This method is also applicable to solid tumors.[28] A drug that causes no obvious cytologic effects in a tumor at sublethal doses may produce significant effects when given at supralethal doses.

An *egg-culture method* has been described in which the test object is the Sarcoma 180 (a mouse tumor) growing on the chorioallantoic membrane of the chick embryo.[28] The tumor fragment is implanted on the eight-day embryo; when the presence of an active growth is demonstrated four days later, the maximal dose of the test chemical tolerated by the egg is injected into the yolk sac. Five days after injection the Sarcoma 180 is removed and examined for size, histologic appearance and viability, by transplantation into mice. The method, although limited in application, permits a comparison of the effects of chemicals on a variety of actively growing embryonic and tumor tissue; it may also reveal differences in the inherent susceptibilities of mouse and chick tissues.

Tumors in fowls are usually associated with a filtrable agent. The Rous sarcoma virus has most frequently been used in chemotherapeutic studies. It may be implanted in young chicks[29] or on the chorioallantoic membrane of the chick embryo,[30] and the number of "takes" and rate of tumor growth measured. Another technic is the determination of the concentration of the test substance in vitro that is necessary to inactivate the infectivity

*The smallest amount of the drug necessary to kill 50 per cent of the animals within the test period.

of the virus. Similar studies have been conducted with fowl leukosis in chicks.[31]

Several types of technics have been used in vitro to measure the toxicity of certain agents to neoplastic cells, or to detect a selective toxicity to neoplastic tissue by comparison with normal tissue of similar origin. These procedures are particularly useful when only small amounts of the test substance are available.

Tissue culture. Normal and neoplastic cells are explanted under similar conditions, and the effects of the test substances, as measured by their lethal effect or a specific type of cellular injury to the explant, are determined. The susceptibility of normal and neoplastic cells to the test substance is compared, and the procedure may reveal an agent selectively injurious to neoplastic cells. Ormsbee, Cornman and Berger[32] have described a method of grading the condition of explanted tissues, so that a numerical index of injury can be obtained. The ratio between the injury produced by a given agent in the neoplastic and in the normal tissue is known as the "selective index."

Chemical toxicity. Sugiura[33] and others have placed small pieces of mouse tumor in a solution of the test agent for a prescribed period at certain temperatures (one test is run at 2 to 4°C. for twenty-four hours), after which the fragments are assayed for viability in susceptible mice. The index of effect is the percentage of "takes" and their rate of growth. This method measures the toxicity of chemicals to cells, but it provides no evidence for a selective effect on tumor cells. Another variation in this method is to place slices of tumor tissue and of normal liver tissue in serum containing the test substance at 37°C. for twenty-four hours and then to examine the tissues histologically.[34] A selective effect is shown if the normal tissue appears unaltered in the presence of damaged neoplastic tissue.

Metabolic studies in vitro. Suspensions or slices of normal and neoplastic tissue are placed in the Warburg apparatus, and the test substances are added. Selective inhibition of the tissue respiration of the neoplastic compared with the normal tissue is the measure of effect.[35]

None of the methods in use appear to be entirely satisfactory in disclosing agents that have a selective action on tumor cells. One of the important fields in cancer research is the development of more precise methods for testing substances in the laboratory for chemotherapeutic activity.

Clinical Testing of Chemotherapeutic Agents

The clinical investigation of various substances for therapeutic activity in cancer still remains, in large part, a program distinctly separate from the laboratory "screening procedures." Most of the laboratory procedures are designed to disclose substances that are selectively injurious to tumor cells, either temporarily damaging, or inhibiting, or destroying neoplastic cells in the presence of normal cells. The discovery of such substances in the laboratory and subsequent proof of their effectiveness in patients with cancer would be of extreme importance to the clinician. In the meantime, the clinician is faced with the problem of palliating or attempting to control definite clinical entities that fall in the category of neoplastic diseases. He cannot depend entirely on the laboratory "screening" results to give him substances for therapeutic trials; he must be able to borrow from the fields of biochemistry, pathology, physiology, pharmacology, endocrinology and toxicology. For example, certain cancers may be controlled by influencing the nonneoplastic properties of cells persisting from their tissue of origin; this technic is particularly effective if the tissue from which the cancer arises is not essential to life. Without undue injury to the organism, the prostate may involute almost completely, in some cases, with stilbestrol therapy, or the thyroid gland may be severely damaged by radioactive iodine through its ability to concentrate iodine selectively; if cancers, arising from these tissues, retain their characteristic physiologic properties they will also be adversely affected by these agents. General cell poisons may depress certain neoplastic cells to a greater degree and for a longer period than they depress the normal tissue of their origin and, thereby, produce some clinical benefit. Secondary manifestations of tumor growth may be combated by general therapeutic measures appropriate for the organ or system involved or for the physiologic derangement present. The clinician will therefore obtain suggestions for clinical trials from many sources, of which a relatively limited one, at present, is the laboratory screening program.

If a compound is to be studied clinically, pharmacologic data and, if obtainable, the mechanism of action in vivo should be available before the treatment of patients is begun. It is apparent that a more complete, coherent and critical clinical study can be carried out if there is some indication of how the patient and disease will be affected by the agent. Experience has shown that the clinical evaluation of an agent producing only palliative effects may be an extremely difficult project; an effective form of therapy may be overlooked owing to an inadequate clinical trial, and ineffective treatments have been used for many years because of the lack of a convincing body of negative data. These problems are well known to clinicians familiar with cancer, and they have recently been discussed in detail.[36]

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 34321

PRESENTATION OF CASE

A fifty-five-year-old businessman entered the hospital because of abdominal pain and vomiting.

One night six weeks before admission the patient awoke feeling nauseated and subsequently vomited several times. There was no pain. Business and family worries had been plaguing him and for several months he had felt tense and nervous. After this episode he remained in bed four days and then returned to work. Late at night, following days on which financial problems had been particularly trying, spells of painless vomiting would recur. Two weeks before admission he left work. The nocturnal vomiting became more frequent and began to be accompanied by severe cramps, starting in the back and radiating around to the midline in a vise-like manner. He was given pills and put on a bland diet without relief. Two days before admission the frequency of vomiting increased to every two or three hours; no food or fluid was retained. The vomitus consisted of food, fluid and mucus without blood. The bowels had been moving only with laxatives or with enemas. The stools were of normal color. During this illness there was a 25-pound weight loss.

During examination the patient was tense and uncomfortable, constantly shifting position in an effort to relax. When activity reached a peak, he vomited. The speech was rambling, and he had difficulty recalling dates and time. The heart was normal. There was dullness over the left lower lobe posteriorly and in the left axilla, breath sounds and tactile fremitus being reduced in the same areas. The abdomen showed tenderness and spasm throughout the epigastrium. Peristalsis was active. There were no masses.

The temperature was 98.6°F., the pulse 88 and the respirations 20. The blood pressure was 135 systolic, 90 diastolic.

Examination of the blood revealed a white-cell count of 9600. The hemoglobin was 14.6 gm. There was a + test for albumin in the urine, and rare casts were found. The icteric index was 13.

The patient was tense and frequently nauseated but appeared to obtain considerable relief from hot baths so that he stopped vomiting and was able to drink water. On the third hospital day the skin and scleras were slightly jaundiced. A surgical consultant found a tender mass in the epigastrium, extending to both sides of the midline but slightly more to the left. The edges of the mass were indefinite; the whole mass was about 15 cm. in diameter. Rectal examination was negative. On the same day the gastrointestinal series showed some thickening of the gastric folds, and there was evidence of pressure along the lesser curvature and the posterior wall. The duodenal loop was enlarged; the second portion was displaced to the right and showed evidence of somewhat lobulated compression from the region of the pancreas, which also displaced the third portion of the duodenum downward. There were several diverticula in the colon. The spleen was enlarged. There was considerable fluid in the left pleural cavity. Linear areas of atelectasis showed in both lower lobes of the lungs, and motion of both leaves of the diaphragm was slightly limited. On the following day the icteric index was 25, and the serum amylase was 78 units per 100 cc. Three hundred and fifty cc. of opaque, amber fluid, which proved to be sterile, was removed from the left chest. The temperature remained normal.

An operation was performed on the fifth hospital day.

Differential Diagnosis

Dr. Perry Culver: In discussing this case I shall start with certain features that stand out as signposts toward arriving at a diagnosis. The first is a mass in the upper abdomen, in the region of the pancreas, if we can believe what the x-ray examination appeared to show. Perhaps at this time we should view the films to see if my conception of this mass is true.

Dr. Stanley M. Wyman: The films of the chest show rather definite pleural effusion on the left. The left main bronchus is perhaps displaced slightly downward. One can see no definite defect in its lumen. There is some atelectasis at the right base, and the changes in the left are probably partially the result of considerable atelectasis in the left lower lobe. The heart shadow does not appear definitely abnormal. The most striking change in this patient's examination lies in the duodenal loop, which is displaced laterally in the second portion and manifests a fairly constant contour in this region. Two spot films of that area confirm this impression and show what appears to be a somewhat lobulated mass pressing into the lumen at this point. Downward displacement of the third portion of the duodenum is seen. The displacement of the stomach I cannot see on these films but it may have been seen by the fluoroscopist. The large spleen extends downward to this point. I can see no evidence of actual bone destruction.

Dr. Culver: Can you see evidence of metastasis anywhere in the lung to account for the fluid?

Dr. Wyman: No; simply fluid, without definite evidence of intrinsic disease except for atelectasis.

Dr. Culver: The discovery of this mass three days after the initial physical examination when no mass had been found makes one wonder if this tender mass in the midepigastrium appeared suddenly overnight.

The second salient point is the sudden appearance of jaundice. Since the mass is in the general region of the common bile duct, the possibility of obstruction of the duct is suggested.

The third point that one has to bring into the picture is the rather marked weight loss of 25 pounds in approximately six weeks. Apparently the patient had retained most of the ingested food until two days before admission, so that he did not lose the 25 pounds because of limited food intake or from vomiting.

The fourth point is the fluid in the left chest. These four facts have to be reconciled with what was apparently a consistently normal temperature, a normal white-cell count, and no anemia. We also have to try to fit the enlarged spleen into the picture.

When I read this abstract over, I immediately thought that the mass, the jaundice and the marked weight loss were the three salient points for carcinoma of the pancreas. One can add to such possibilities that of fluid in the left chest from metastasis to the pleura. Then, because of the sudden appearance of the mass in the midepigastrium, where no mass had been felt three days before, one could postulate that there was sudden development of a cyst of the pancreas. It is rather common for a cyst of the pancreas to develop on the basis of carcinoma. I would like to speculate that there had been a hemorrhage or bleeding into the cyst to account for its rapid increase in size. While carcinomas of the pancreas are statistically one of the common causes of painless jaundice, approximately 50 per cent of all carcinomas of the pancreas cause pain. Many cause back pain, which is most severe. Often an erroneous diagnosis of psychoneurosis is made because no one can explain the back pains until the diagnosis finally becomes evident post mortem.

If these were all the facts, the diagnosis would be easier, but we have to consider other things. What is the relation of his mental status to the symptomatology? The business and family worries gave this man a perfect background for peptic ulcer. The psychosomatic experts on duodenal ulcer say that people with the ulcer type of personality remain asymptomatic as long as either their business or their family life runs smoothly. When both are disturbed ulcers develop. This man had both things to plague him. The fact that he had a recurrence under stress also suggests an ulcer. In addition, the

crampy pains in the back suggest penetration of an ulcer in the pancreas. The tenderness in the epigastrium can again be caused by a penetrating ulcer. Many hold an opinion that tenderness does not occur with a duodenal ulcer until there is penetrating involvement of either the pancreas or peritoneal surface of the duodenum. So much for the ulcer. It will not explain such things as the fluid in the chest, the mass in the midepigastrium, and probably the jaundice.

What next? Gallstones should be considered. The patient had recurrent pains in the back and whenever one elicits this fact one must think of gallstones as well as peptic ulcer. Moreover, with this recurrent periodic pain there was associated nausea and vomiting. If jaundice appears, it is even more suggestive of gallstones obstructing the common duct. Unfortunately, there should have been fever and leukocytosis for the diagnosis of gallstones. Unless there were complications from the gallstones, he should not have had this mass in the midepigastrium and the fluid. One could suggest that the gallstone had perforated into the lesser omental cavity, and that the patient then developed an abscess of the lesser omental cavity. It could then cause inflammatory obstruction of the common duct and perhaps extension of fluid through the left leaf of the diaphragm. We might even consider that because of this mass the splenic vein had been involved with thrombosis and, ergo, a large spleen. It is a good story but we have no elevation of the white-cell count and no fever to go with it.

Another possibility is that a person with severe pain in this region and a mass, which might be a pancreatic cyst, could have chronic recurrent pancreatitis or acute pancreatitis. So far as acute pancreatitis is concerned, this man was sick enough but he did not have a high white-cell count; he did not have a high temperature; he had no board-like abdomen — in fact, nothing to go with acute pancreatitis except for the serum amylase of 78 units. In this hospital the serum amylase is so variable that we cannot put much emphasis on a single determination. If we had had another determination, either twelve or twenty-four hours before that, and if it had been approximately 30 units, or another twenty-four hours later and had it been around 125 to 150 units, we could say that the serum amylase was significant. This 78 units was an isolated reading. A determination of 50 or 55 units is considered the upper limit of normal. With an amylase of 78 units if we wanted to "go out on a limb," we could say that this man had pancreatitis. So we are left somewhat in a quandary.

I have covered the essentials of my differential diagnosis and I still have not considered one point, that is, the rambling speech and difficulty in recalling dates and time. I am frankly stumped as to how to explain these neurologic changes. It is possible that excessive electrolyte depletion due to the vomiting was the basis for this neurologic manifestation. We know that some decompensated cardiac patients, who are treated intensively with salt restriction and dehydration, are "out in left field" because of hyponatremia.

I am sure I shall be wrong but I am going to say that he had carcinoma of the pancreas, with possible involvement of the splenic vein and thrombosis to explain the enlarged spleen, metastases to the left pleura to explain the fluid in the left chest and that he developed a cyst of the pancreas, secondary to the cancer.

Clinical Diagnosis

Acute pancreatitis?

Dr. Culver's Diagnoses

Carcinoma of pancreas.
Pancreatic cyst.
Metastatic cancer of left pleura.
Splenomegaly due to thrombosis of splenic vein.

Anatomical Diagnoses

Carcinoma of pancreas, with extension to stomach, transverse colon, and spleen, with metastases to retroperitoneal lymph nodes, lungs and kidney.
Hydrothorax, bilateral.
Pulmonary atelectasis, left lower.
Operations: cholecystostomy and jejunostomy.

Pathological Discussion

Dr. Benjamin Castleman: The preoperative diagnosis was acute pancreatitis. The surgeon found a large amount of bloody fluid in the abdomen and extensive induration of fat, especially along the lesser curvature of the stomach, with small nodules more suggestive of fat necrosis than carcinoma. The liver appeared normal. The spleen was twice the normal size to palpation, but it was not visualized. The gastrocolic omentum was opened and the pancreas carefully palpated. It was enlarged and indurated throughout. The gall bladder seemed thick, but he did not believe that it was diseased. A cholecystostomy and a jejunostomy were done — the latter for feeding purposes.

A biopsy of one of the nodules that the surgeon thought might be fat necrosis turned out to be carcinoma, but we could not tell where the tumor was primary.

The patient died a few days later, and at autopsy we found the stomach fairly well fixed. On the lesser curvature and the posterior wall was a large mass that extended to the left, up to the hilus of the spleen. All the retroperitoneal nodes along the aorta and beneath the stomach were involved with tumor. On opening the stomach we found that the mass adherent to the posterior wall did not involve the mucosa and was entirely extrinsic. The mass proved to be the pancreas involved from head to tail with

cancer. The tumor had extended into the spleen and what was believed to be a large spleen was spleen plus tumor. The tumor had also extended to the transverse colon and microscopically there were metastases to the lung and kidney. The shadow in the left-lower lung field seen on the x-ray examination was 2 liters of clear fluid with compression atelectasis of the left lower lobe. There was also a liter of fluid in the right pleural cavity. An interesting incidental finding microscopically was an islet of Langerhans in the pancreas about five times the normal size. It may have been a section through a small adenoma that was not recognized grossly because of the widespread carcinomatous invasion.

Unfortunately we were not permitted to examine the brain, but it is not uncommon for patients with carcinoma of the pancreas to have mental symptoms without evidence of cerebral metastases. Why, no one knows.

A PHYSICIAN: Was a blood sugar done?

DR. CASTLEMAN: No. The urine did not contain any sugar.

A PHYSICIAN: How about the nonprotein nitrogen?

DR. CASTLEMAN: It was normal. I believe that the elevated amylase can be explained by the extensive involvement of the pancreas by tumor.

DR. CULVER: The more of these cases we see, the more I am impressed with how varied and bizarre the symptomatology can be. I remember one case that I saw in consultation as a problem in vitamin deficiency because the patient had numbness and tingling of the toes. He had been treated with larger and larger doses of vitamins without relief of his peripheral neuritis. He also had pain in the back. No one paid any attention to it. When he died a year later a carcinoma of the pancreas was found at autopsy as the probable cause of the difficulty. A great many of these people who have carcinoma of the pancreas are diagnosed as psychoneurotics for a period of time. They have vague backaches, the x-ray films are normal, and they have all sorts of symptoms, but no one is able to fit them into any syndrome. One should become sensitized to the possibility of carcinoma of the pancreas. How to prove it is another story.

DR. CASTLEMAN: It is interesting that the man who interpreted these x-ray films originally concluded: "The findings are those of a mass in the region of the pancreas. I would think that the entire pancreas was involved and although carcinoma cannot be definitely excluded, pancreatitis with involvement of the lesser omentum would be my first choice." That is what probably influenced the surgeon in making the preoperative diagnosis.

DR. CULVER: Was the mass cystic or solid?

DR. CASTLEMAN: It was a very necrotic tumor.

DR. CULVER: That is probably the reason it was tender.

CASE 34322

PRESENTATION OF CASE

A thirty-seven-year-old Negro was admitted to the hospital complaining of progressive blindness, proptosis of the left eye and pain in the left supraorbital region.

One month prior to entry he was admitted to another hospital with similar complaints of about one week's duration. A note from that hospital concerning the patient reported that x-ray examination had revealed sinusitis. X-ray studies of the skull were negative. A spinal puncture revealed normal pressure and cell count, with a negative globulin reaction. The gold-sol curve was 0000000000. The Wassermann reaction was positive. A blood culture was negative. Two weeks following admission to the other hospital an acute epididymitis developed and he was subsequently transferred to this hospital.

On physical examination the patient was obviously acutely ill. There were proptosis of the left eye and complete bilateral nasal obstruction, with a cheesy purulent material in the vestibules. A left external ethmoid incision was present, and the sinuses were dark to transillumination. The soft palate was pushed downward and forward, and the soft and hard palate were both swollen and indurated. A Caldwell–Luc incision was present on the left side. The chest and abdomen were negative. The left testicle was enlarged to about the size of a small orange and did not transmit light. Examination in the Eye Clinic revealed retention of ability to project light accurately in the right eye, with total blindness on the left. Impairment of ability to move the eyes laterally and some loss of power to move the muscles supplied by the seventh nerve were also noted.

The temperature was 103.4°F. The blood pressure was 90 systolic, 60 diastolic.

Examination of the blood showed a red-cell count of 3,680,000, with 11.8 gm. of hemoglobin, and a white-cell count of 6300, with 75 per cent neutrophils. The urine sediment contained 8 to 10 white cells per high-power field. Spinal puncture revealed an initial pressure equivalent to 170 mm. of water, with a total protein of 172 mg. per 100 cc. The sugar was 63 mg. per 100 cc., and a cell count showed 480 white cells per cubic millimeter, with 39 per cent polymorphonuclears and 61 per cent lymphocytes. A gold-sol curve was 0011233210. X-ray films of the chest were normal. Those of the skull disclosed no enlargement of the sella turcica. X-ray examination of the sinuses revealed that the cell partitions of the ethmoid sinuses were gone and all sinuses showed a soft-tissue density. A large nasopharyngeal mass extended anteriorly into the nasal cavities. All sinuses, including the sphenoid, were full. Cultures from the nose, throat and left ethmoid showed *Staphylococcus aureus*.

Following admission the patient's condition grew steadily worse, he became disoriented, and x-ray therapy was started. The patient improved somewhat for a short time but after about two weeks began to suffer from abdominal distention. He became steadily weaker and died after approximately one month in the hospital.

Differential Diagnosis

Dr. Grantley W. Taylor: I am probably here because I know very little about tumors of the nose and throat and eye. This is fairly obviously a problem of neoplasm. It is worth while to make a few general remarks on the subject because I cannot go into the elaborate details of histology in these cases.

This thirty-seven-year-old man had a rather acute course. The first evidence of anything wrong, from his viewpoint, was progressive loss of vision and proptosis of the eye and pain in the superior orbital area that initially took him to another hospital, where, I presume, a diagnosis was made of chronic infection involving the accessory sinuses, probably primarily the ethmoid. We see this evidence of ethmoid disease in an occasional case, namely, disturbance of vision and proptosis of the eye and headache. It is consistent with a diagnosis of infection. However, the findings at the other hospital were not consistent with the diagnosis of infection primarily. He had a normal chart and a normal leukocyte count, and even if it was obvious that the disease was more in the nature of a chronic noninflammatory process, the evolution was rapid after he entered the other hospital. He had two operations; one, we know, was an ethmoid operation, the scar of which was visible when he came here. The other was a Caldwell–Luc incision. By the time he arrived here there was no question that he had tumor of marked extent. The palate was pushed downward, the nares were obstructed, and there were blindness of the left eye and proptosis. Obviously he had a tumor mass originating in the general vicinity of the nasopharynx or the ethmoid area, with probable direct extension into the orbit and probable further extension through the orbital foramen into the base of the skull. When he came here he had a great deal of evidence of neurologic disturbance around the head and base of the skull, which could be interpreted not so much as due to pressure from the tumor as probably the result of direct invasion. He had no elevation of white-cell count but he had a temperature. He had a gold-sol curve and white cells in the spinal fluid, and we must assume that he had a direct local meningitis due to progress of the tumor and introduction of infection through the base of the skull.

I should like to look at the x-ray films and have Dr. Wyman point out the soft-tissue masses that are described. Interpretation of x-ray films of the sinuses is a highly specialized art.

Dr. Stanley M. Wyman: The soft-tissue thickening in the posterior nasopharynx is best seen in the lateral view and is confined chiefly to the roof of the nasopharynx in this area. There is soft-tissue density extending upward and obliterating the normal ridges of the sphenoid and wiping out completely the normal cell partitions in the ethmoid sinuses. With a strong light one can see soft tissue extending far forward into the posterior nares. There is probably some haziness in the frontal sinuses, although this is less definite. A frontal projection shows density in both ethmoid sinuses, with complete loss of the cell walls and probably some hazy density in the frontal sinuses. This position shows a soft-tissue density overlying the left orbit, a fairly definite mass extending upward where the left eye is being pushed forward. A view of the floor of the skull shows density in both ethmoid sinuses of rather uniform, hazy character, showing only a small airway far posteriorly. I can see no definite bone destruction, however.

Dr. Taylor: We are confronted with a rapid evolution of a large tumor mass that fills the nasal passages, the nasopharynx and the accessory sinuses and that has destroyed bone, and it seems to me that the only conclusion one can derive is that we are dealing with a rapidly growing and highly malignant neoplasm. What is the nature of it? When this point is reached all one can say is that the answer is something the microscope alone can give. We have a number of rapidly growing and highly malignant tumors that may occur in this area. They may be primarily carcinoma, ordinarily either in the sinuses or in the pharynx, and there are also sarcomas seen in this area. Which of these we are dealing with in this case is largely a matter of guess. It is interesting that although there is no specific description of the neck, we can probably assume that there is nothing in the way of metastases to the regional lymph nodes. We know that these rapidly growing carcinomas in this general area are prone to form early bilateral cervical-lymph-node metastases. We have an x-ray examination of the

chest during the terminal illness, which showed no evidence of dispersion of the disease. Both these factors, I think, argue considerably against a carcinoma and in favor of a sarcoma. It is largely a matter for the pathologist to decide.

The clinician was confronted in this case with the problem of what to do about it. Quite obviously with disease as extensive as that described here in the physical examination and as revealed by x-ray study, the only hope was that we were dealing with a tumor highly sensitive to radiation. Accordingly, this method of treatment was undertaken, in spite of which there was no particular improvement. It seems to me that if this sarcoma, as I have said, was of the lymphocytic series, Hodgkin's disease or lymphoblastic type, there would probably have been an initial very gratifying and rapid response. Such does not seem to have been the case. It seems, therefore, more reasonable to say that this is perhaps a sarcoma of the neurogenic group — a neurofibrosarcoma or a glioma or one of those tumors.

I cannot go very much farther than that, Dr. Mallory. The lesson, I think, is that when anybody has a bizarre cold with sinus infection that does not respond to ordinary, reasonable measures, the possibility of a diagnosis of neoplasm should be entertained. The more we look for this the more likely we are to find it at an early stage. In this case even if the diagnosis had been made initially, the man's "goose was cooked."

DR. TRACY B. MALLORY: I think the abstract is misleading. There is a note to the effect that the local tumor had responded fairly well to radiation, but two days later the patient died.

DR. TAYLOR: I still will be glad to hear what you found.

A PHYSICIAN: How about the possibility of tumor primary in the testicle with metastasis to the brain, such as a chorioepithelioma?

DR. TAYLOR: It is nice of you to bring it up. I wondered if we should discuss the possibility of metastatic carcinoma. It is highly unlikely. We have, in a few cases, seen that occur — localized metastatic neoplasm. I did not consider this necessarily a tumor of the testis, even though it did not transmit light. He had an acute epididymitis two weeks after admission to the other hospital. In other words, we could say that the testicle was innocent at the time of the initial physical examination, when the disease in the nasopharynx was well along. That is the only physical finding other than the local one that could be implicated. One could also say that he had a renal-cell carcinoma with a solitary metastasis and never showed anything in the kidney. That is also possible, but we would not be dealing with the facts as presented.

A PHYSICIAN: Can you rule out gumma in view of the positive Wassermann test?

DR. TAYLOR: I gave some thought to gumma but was inclined to pay not a great deal of attention to it. I do not believe that a gumma would evolve so rapidly and give rise to such an extensive soft-tissue mass as he had. I am not expert enough in relation to the gold-sol test and that sort of thing to say that the gold-sol curve is not consistent with a syphilitic disease. But it seems to me that he suffered from probable pyogenic localized invasion of the meninges around the base of the brain, which accounted for some of the seventh-nerve weakness and the impaired ocular motor functions on the other side and so forth.

DR. JOSEPH C. AUB: I did not see this patient but I am intrigued by Dr. Taylor's discussion of the metastases. Are not tumors in this area prone to go to the brain? Do you not believe that this was a metastasis to the brain?

DR. TAYLOR: I would say direct extension rather than metastasis.

DR. AUB: The x-ray therapy might well have been of influence.

DR. TAYLOR: You mean on the ground that x-ray treatment might have made it worse?

DR. AUB: Yes; it may have facilitated the spread of infection.

DR. TAYLOR: He had this ethmoid trouble before x-ray treatment was started. As I read it I thought that the infection was already there. Whether x-ray therapy would facilitate the transmission of infection, I do not know.

DR. WYMAN: It is quite consistent, as Dr. Taylor said, with a malignant lesion in the posterior nasopharynx invading the sinuses, and from the point of view of x-ray therapy one can go no farther than to say that it is probably malignant neoplasm.

CLINICAL DIAGNOSIS

Malignant tumor involving nasal chambers, ethmoid and sphenoid sinuses, left lateral and anterior nasal walls, nasopharynx, hard and soft palate and left periorbital tissue.

Dr. Taylor's Diagnosis

Sarcoma, type undetermined.

Anatomical Diagnoses

Malignant lymphoma (stem-cell type), with involvement of nasopharynx, air sinuses, left orbit, base of skull, retroperitoneum, left testicle, left kidney and pancreas.

Extradural abscess, right middle fossa.

Pathological Discussion

Dr. Mallory: A biopsy of this tumor was done before x-ray treatment was started. I did not confuse Dr. Taylor with that because our report on it was that the tumor was extremely variable in appearance. In some areas it suggested plasma-cell myeloma, in other areas neuroblastoma, and in still other areas lymphoblastoma. We were unable on the biopsy to make any diagnosis more specific than extremely malignant neoplasm.

At autopsy we found this large tumor mass involving the entire nasopharyngeal region and the sinuses. It had partially eroded and markedly thinned the bone at the base of the skull, particularly the wings of the sphenoid, and extended into the orbit and the nares. The blindness was due to a direct involvement of the optic nerve. We also found considerable tumor elsewhere in the body. The testis was involved with tumor and all the retroperitoneal tissues were a massive sheet of tumor. Tumor infiltration had obliterated all the retroperitoneal lymph nodes surrounding the aorta, had encapsulated both adrenal glands, invaded the kidneys at one spot, and surrounded and invaded the pancreas. The only suggestion of this extensive abdominal involvement in the physical examination was the vague description of distention of the abdomen. There was enough tumor in the retroperitoneal tissues to explain the distention, and I imagine no isolated tumors could be felt.

From the histologic appearance of the tumor, the diagnosis is still, I think, a matter of some question. The distribution puzzled us quite a bit; it was essentially the distribution of lymphomatous tumor and the histology is consistent with that. We finally called it a reticulum-cell sarcoma of a very undifferentiated type. The possibility of plasma-cell myeloma was seriously considered at autopsy because the nasopharynx is the one spot in the body where plasma-cell myeloma or plasmocytomas are common outside the bone marrow. There was, incidentally, diffuse involvement of the bone marrow with multiple small foci of tumor.

Dr. Taylor: He did not have an anemia so marked as to suggest that type of disease?

Dr. Mallory: The anemia may have progressed during his stay in the hospital. I think we have very little evidence on that. During all the early period in the first hospital, and even for several days in this hospital, this was considered to be an inflammatory process. The possibility of sinus thrombosis was seriously considered and the thought of neoplasm occurred a little bit later. There was secondary infection of the tumor and this infectious process had extended through the sphenoid and produced a localized, extradural abscess, but there was no true meningitis.

Dr. Bernard M. Jacobson: Was the spleen involved?

Dr. Mallory: No.

Dr. Taylor: The superficial lymph nodes of the neck were entirely free?

Dr. Mallory: Yes.

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THE THYROID NODULE

MUCH of the recent literature concerning the thyroid gland has emphasized the conflicting opinions that exist regarding the incidence of carcinoma of this structure, and the interpretation of the nodule in the gland as precancerous. On the one hand reports from surgical clinics where an aggressive attitude is followed disclose that carcinoma is discovered in a large percentage of apparently innocent nodules; opposed to this are the analyses of routine autopsy material indicating a very low incidence of thyroid carcinoma as a cause of death. A further complication enters the picture with the disagreements among pathologists in interpretation of borderline conditions, adenomas with blood-vessel invasion, carcinoma in aberrant thyroid tissue and benign metastasizing goiter. The impartial observer is brought to the conclusion that a wide disparity exists between histologic character and clinical behavior or, alternatively, that carcinoma of the thyroid gland is readily curable in the earliest stages, when the disease is not recognizable clinically.

Currently, evidence of cancer is found in about 20 per cent of the single nontoxic nodules that are removed surgically at the Massachusetts General Hospital. This high incidence of thyroid cancer may be contrasted with the experience at the Pondville Hospital, where only 46 cases have been encountered in twenty years, or approximately 1 case among every 300 cases of all types of cancer.

There is general agreement that the highest incidence of cancer is found in the single nontoxic adenoma, although all types of thyroid disease have been associated with carcinoma. At the Pondville Hospital more than 10 per cent of the thyroid carcinomas have arisen in toxic goiters.

The paper of Anglem and Bradford published elsewhere in this issue of the *Journal* offers further evidence of the incidence of carcinoma in thyroid nodules, and also sheds some light on the apparently low incidence in autopsy statistics. The study emphasizes the frequency with which carcinoma may be found in an apparently benign nodule. It seems probable that with the increasing employment of medical measures in the management of hyperthyroidism, the incidence of carcinoma in the remaining group submitted to surgery will increase. There is also the possibility that the drugs used in the treatment of hyperthyroidism may in some cases precipitate the development of carcinoma.

Regardless of the role of the nontoxic adenoma, whether it is precancerous or merely indistinguishable from cancer in its earliest stages, there is sufficient evidence to justify prompt surgical intervention in all cases with single nontoxic nodules. Carcinoma discovered at this early stage is curable in a high percentage of cases. The decision to keep such a lesion under observation, and to resort to surgery only when the lesion by rapid growth or fixation raises the probability of malignant degeneration, is a serious one and not in the best interests of the patient. Operation performed when the diagnosis of cancer is obvious results in fewer cures. With thyroid carcinomas as with those of other regions, prompt intervention is likely to be successful. The nature of the nodule should be decided in the laboratory, not on its future course in the neck of the patient.

THE BOSTON EYE BANK

THE Boston Eye Bank, affiliated with the Eye-Bank for Sight Restoration, Incorporated, of New York City, has been in operation for the past year and a half. The wisdom and foresight of those responsible for its establishment are attested by the number of people who have benefited from corneal transplantation through its services.

Naturally, the dramatic element in corneal transplantation has great popular appeal, and this has been reflected by the gratifying interest demonstrated by the public and lay press in the activities of the Eye Bank. Numerous requests are received daily for donation forms bequeathing eyes. However, at present it is not practical to obtain eyes from other than patients dying in a hospital. It is precisely in this connection that the medical profession, including hospital administrators, can do much to ensure success of this worthy project. Literature is available for reception rooms in hospitals and doctors' offices explaining the noble aims and purpose of the Eye Bank. At the time that permission for post-mortem examination is sought, a proper appeal could well be made, for the eyes.

No exact figures are available regarding the number of blind persons throughout the country who could be aided. The best estimates have been placed at 10,000 to 15,000. Obviously, it will take time and many high-minded persons to provide a sufficient number of eyes to restore that most precious gift, sight, to these unfortunate victims.

If, for some reason, an eye is not suitable for corneal transplantation, it is used in research, particularly in problems that do not lend themselves to solution by the use of animal eyes. For example, studies of the vitreous and the possibilities of vitreous transplantation are currently the object of much research.

In its short span, The Boston Eye Bank has proved a most valuable ally in the fight against blindness. The future is contingent upon the continuing support of the general public and the medical profession.

CHLOROMYCETIN

IN THE field of virus and rickettsial diseases the therapeutic results of the use of chemotherapeutic and antibiotic agents have not been comparable to those obtained in infections with bacterial agents. However, there is accumulating evidence of progress in this field.[1] The sulfonamides and penicillin have been shown to be active against certain viruses of the psittacosis-lymphogranuloma group. Certain rickettsias have proved susceptible to para-aminobenzoic acid, and therapy with this agent has given favorable results in some diseases caused by this group of agents. Streptomycin has also been found to have some rickettsiostatic effect in fertile hens' eggs and also in guinea pigs. Thus far no really effective agent has been found that affects the smaller viruses such as those responsible for the encephalitides and influenza.

Interest at the moment is focused on a new antibiotic, chloromycetin.[2–8] This agent has been obtained in crystalline form from cultures of a Streptomyces similar to the ones that produce streptothricin. It is particularly noteworthy in that a large portion of the weight of chloromycetin is in the form of nonionic chlorine. One of the chief drawbacks of chloromycetin is its low solubility in water, but it is soluble in many solvents that can be used clinically, including propylene glycol. It is highly stable in water over a wide range of reaction and resists boiling.

In vitro this agent appears to be effective in fairly small concentrations against a large range of gram-positive and gram-negative organisms, but moderately high concentrations are required for certain mycobacteria and for a few gram-negative bacilli. It is not effective against fungi, protozoa or rabbit syphilis, but at least one strain of Borellia is extremely sensitive. In vivo it has been shown to be markedly effective against various strains of rickettsias in mice and eggs. It has also been found effective against some strains of psittacosis in eggs and mice, but not against most other viruses. It appears to be inferior quantitatively to streptomycin in mice against many infections and does not seem to have any effect against pneumococcal infections.

One of the great virtues of chloromycetin is that it seems to be effective in mice and dogs when given by mouth. It appears to have relatively low toxicity and, from the results obtained in mice, to be effective even late in the disease. Clinical trials have been undertaken in the treatment of epidemic typhus and in scrub typhus.[9–12] The early results as judged from press reports seem to be favorable, and the details will be awaited with considerable interest.

There is reason to believe that other chemotherapeutic and antibiotic agents with similar or greater effects against many viral and rickettsial diseases will become available in the not too distant future and with those already available will tend to bring under control another large group of serious infections.

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THROUGH THE LOOKING GLASS

THE lonely heart may find its mate in unfrequented byways; trees grow in Brooklyn; stars fell, of all places, on Alabama. Romance emerges where one least expects it. Thus, in the *Bulletin of the United States Army Medical Department*, among such subjects as "Venereal Disease Anxiety" and "The Suddenness with which the Bowel Can Fill with Gas," appears the title, "Veterinary Inspection of Oysters."*

And we had thought that the Army, by now, was fully mechanized.

The term "veterinary," we had been led to believe through all these years by Webster (Noah), is "of or pertaining to the art of healing or treating the injuries and diseases of domestic animals." If by any stretch of the imagination this category can be expanded to include marine or aquatic life we should certainly expect the first candidate for veterinary attention to be the sea horse (genus *Hippocampus*), and its picket lines to be serviced by the Marine Corps, or at least the Navy — or perhaps the whole purpose of the project is to provide occupation for veterans.

That there may be some reason, however, for believing that the oyster leads a double life, rising from the relatively inert existence of a marine bivalve mollusk to an amphibious plane on which it attains a considerable degree of mobility, we can quote no less an authority than the late Lewis Carroll.

Whether or not it was veterinary inspection that they were anticipating, oysters have apparently been known to behave in an extraordinary manner, according to the observations of this great naturalist:

> Four other Oysters followed them,
> And yet another four;
> And thick and fast they came at last,
> And more, and more, and more —
> All hopping through the frothy waves,
> And scrambling to the shore.

The method of locomotion of the succulent bivalve (genus *Ostrea*) is also somewhat reminiscent of the method by which horseflesh gets from one place to another, or wherever it happens to be going:

> "It seems a shame," the Walrus said,
> "To play them such a trick.
> After we've brought them out so far,
> And made them *trot* so quick!"

Nor is this zeal for clinical oceanology confined to the Army Medical Department. According to the report of a special commission investigating the edible shellfish of the Commonwealth of Massachusetts, "both natural and artificial propagation of soft shell clams is necessary and feasible, and . . . there is great need of reclaiming a greater number of shellfish from areas determined to be contaminated."

It might be the better part of wisdom to decide once and for all that areas so resolutely bent on their own contamination should be abandoned altogether, at least for the purposes of raising shellfish.

Further inquiry into the veterinary inspection of oysters, however, reveals that hydrogen ion concentration, not hoof and mouth disease, is the subject of investigation.

Bull. U. S. Army M. Dept. **8**:85, 1948.

MASSACHUSETTS MEDICAL SOCIETY

INFORMATION FROM VETERANS ADMINISTRATION

CERTAIN FEES INCREASED

On April 19, 1948, the Massachusetts Medical Society renegotiated its contract with the Veterans Administration. This contract became effective July 1, 1948 and is similar in every way to the previous contract, except that certain fees have been increased; for example, the Veterans Administration will now pay $3.00 for an office visit, instead of the previous maximum of $2.50. The fee for specialist treatment, except neuropsychiatric treatment, has been increased from $3.00 to $5.00.

$6000 Maximum Payment

During the fiscal year 1948 which ended on June 30, many doctors' earnings from the Veterans Administration were very near the $6000 maximum limit allowed by law. With the new increase in fees as described in the previous paragraph, these doctors run the risk of exceeding their $6000 limitation, if they render the same amount of service during the coming fiscal year. They should, therefore, maintain a fairly accurate record of work accomplished each month. In order to insure that the $6000 maximum will not be exceeded, the doctor should limit his veterans' practice to a total earning of $500 per month.

Reimbursement for services rendered in excess of $6000 per year cannot be made. The salary limitation is based upon earnings during the fiscal year, from July 1, to June 30, and is not based upon the payments made.

Referral of Patients

Occasionally during the course of treating a veteran, a doctor finds it necessary to refer his patient to another doctor for consultation or laboratory work. Whenever this is necessary the Veterans Administration should always be notified in advance. Unless the Veterans Administration is so notified, authorization cannot be given and the veteran may have to pay the consultation fee.

Information Phone for Doctors

Two telephones at the V. A. Regional Office have been set aside for the use of physicians phoning for information. Trained clerks will be on duty from 8:30 a.m. to 5:15 p.m. each Monday through Friday. Call LA 3-7500, extensions 751 and 752.

Treatment Procedure Inaugurated in Massachusetts Now Used in Other States

On July 1, 1947 a new form of treatment authorization and a simplified procedure was tried out in Massachusetts. The response and co-operation received from Massachusetts physicians has been very gratifying. The reduction in the amount of paper work required of each doctor has elicited many favorable comments and has enabled many doctors who formerly were unable to cope with the excessive amount of paper work to participate in the Veterans Care Program. The procedure has also resulted in a net saving of 4,697 clerical man-hours per month at the Boston Regional Office, or the equivalent of twenty-six full-time employees. This is an excellent illustration of co-operation and teamwork eliminating many of the irritating problems frequently encountered in the administration of a large scale program.

On the first of May, the new form and procedure was introduced in Rhode Island, Connecticut, New Hampshire and Vermont, where it also has been favorably received.

Information for Newly Designated Fee Basis Physicians

Within the past few months, over 2000 new fee basis physicians have been approved for appointment by the Massachusetts Medical Society; consequently it is felt that a brief outline of Veteran Administration treatment requirements are in order.

1. The Veterans Administration authorizes out-patient treatment only for disabilities that have been adjudicated as service connected.

2. Except in an emergency the veteran should be required to present the physician with an authorization from the Veterans Administration office, before treatment is begun. If emergency treatment is rendered to a veteran it should be reported to this office within fifteen days.

3. Authorizations are for one calendar month only. If the veteran requires treatment during the following month, authorization should be requested on the yellow third page of the treatment form.

4. The veteran should be treated only for the specific disability covered by the authorization.

5. All reports of treatment and completed invoices must be submitted no later than the fifteenth of the month following the month in which treatment was rendered.

6. If medicine is prescribed the prescription blanks that are part of the second or pink page must be used. The veteran may have the prescription filled by any druggist who is a member of the Massachusetts Pharmaceutical Association. The druggist in turn will be reimbursed by the Veterans Administration, through the State Association.

7. Prescribe only for the service connected disability shown on the authorization and only during the treatment period.

8. When forwarding completed reports to this office, retain the upper portion of the yellow or third copy for your files.

9. To identify payments received, the number listed on the reverse side of the voucher form, which accompanies the check, should be compared with the large number appearing on the yellow copy of the treatment authorization, retained by the doctor, in the box headed Fiscal Symbols.

10. If a physician believes that the number of treatments authorized is not sufficient for the month, or if the number of treatments authorized is less than the number requested, this office should be advised, giving a summary of treatment to date and a plan of future treatment, together with prognosis. The doctors authorizing these cases seldom see the patient and must rely almost entirely upon the reports submitted by the contracting physician.

11. All forms must be prepared in ink, typewriter or indelible pencil.

12. All reports of treatment and invoices must be personally signed by the doctor.

Veterans Administration
17 Court Street Regional Office
Boston 8, Massachusetts

DEATHS

Ledbury — John W. Ledbury, M.D., of Uxbridge, died on February 20. He was in his seventy-third year.

Dr. Ledbury received his degree from College of Physicians and Surgeons of Baltimore in 1905. He was an affiliate fellow of the American Medical Association.

His widow, a daughter and two grandsons survive.

Strong — Richard P. Strong, M.D., of Boston, died on July 4. He was in his seventy-sixth year.

Dr. Strong received his degree from Johns Hopkins University School of Medicine in 1897. He was professor of tropical medicine, emeritus, at Harvard Medical School and was a member of the Association of American Physicians and a fellow of the American Medical Association.

A sister survives.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

RHEUMATIC FEVER FELLOWSHIPS

The United States Children's Bureau has made available through the Massachusetts Department of Public Health and the Harvard Medical School two fellowships in Rheumatic Fever at the House of the Good Samaritan of the Children's Medical Center, Boston, for the year beginning July 1, 1948.

Trainees should be interested in working eventually in the field of rheumatic fever in public health or in teaching, rather than in private practice.

Work under these fellowships will probably be acceptable for credit by the Board of Internal Medicine or the Board of Pediatrics.

Application should be made to Dr. Benedict F. Massell at the House of the Good Samaritan, 25 Binney Street, Boston 15, or BE 2-3002.

MISCELLANY

AMERICAN COLLEGE OF CHEST PHYSICIANS

Dr. Richard H. Overholt, of Brookline, took office as president of the American College of Chest Physicians at the fourteenth annual meeting of the College, June 17–20.

CORRESPONDENCE

MORE ON ADOPTION

To the Editor: I am delighted to see the editorial in the *Journal* of June 17 commending the work of the Boston Children's Friend Society on adoption and so indicating the importance of more and more care in this matter.

The New England Home for Little Wanderers has been receiving into custody and placing children for adoption since 1865. With the passing of the years we have become more and more conscious of the importance of great care in procedure. We are sure that physicians, public-health officers and hospitals with whom we have co-operated have realized the protection we can give both children and family in the adoption process. Our staff is equipped with pediatrician, psychologist and psychiatrist, as well as with social workers, to assure a thoroughgoing service. During the past twelve months we have placed with a view to adoption 24 children and have completed the adoption of 35 children who had been placed for a year or more. We are acquainted with many fine young men and women who were placed for adoption as long as twenty-five or thirty years ago. Our experience confirms your statement: "Few decisions require more tact and skill than the suitable placing of a child unwanted under one roof, so badly wanted under another."

CHENEY C. JONES
Superintendent

New England Home for Little Wanderers
Boston, Massachusetts

BOOK REVIEWS

Stethoscopic Heart Records. By George D. Geckeler, M.D. An album of four double-faced twelve-inch phonograph records. New York: Columbia Records, Incorporated, 1948. $8.00.

While a book of records does not suggest the type of literature that is customarily reviewed in medical journals or elsewhere, stranger things are taking place in our brave new world where the electric impulse is used to convey both visual and auditory sensations, and the printed word may yet become the archaic symbol of another forgotten civilization.

This new issue of Stethoscopic Heart Records, ably presented by Dr. Geckeler, provides a most satisfactory reproduction of a wide range of heart sounds, both normal and abnormal, including the arrhythmias and a variety of commonly encountered murmurs.

Although they are intended primarily for the practicing physician who wishes to keep his stethoscope ear in practice, these recordings will fill a variety of academic needs as well.

Human Gastric Function: An experimental study of a man and his stomach. By Stewart Wolf, M.D., and Harold G. Wolff, M.D. With a foreword by Walter B. Cannon, M.D. Oxford Medical Publications. 8°, cloth, 262 pp., with 55 illustrations. New York: Oxford University Press, 1947. $5.00.

The first and second editions of this book are continuations of the studies begun by Beaumont one hundred years ago on Alexis St. Martin, through a gastric fistula, on digestion in the stomach, the composition of gastric juice and the contractions and emptying of the stomach, but are far more complete and interesting and easy to read than Beaumont's "Observation and Experiments" and more useful at present, when men are interested in the causes of ulcer and gastritis, the reasons for their recurrence and the effect of the mind on the stomach.

Great care and skill and ingenuity have been shown in this study. The changes in appearance of the gastric mucosa in severe emotion, the great increase in gastric secretion when the patient was worried, excited or obstinate, the rate of emptying of the stomach and the rapidity with which these changes came and went are described in a clear, simple and convincing way.

The influence of many agents — foods, drugs, coffee, tobacco, alcohol, acids, antacids, atropine, nitrites, histamine, epinephrine, methylcholine, prostigmin, pitressin, benadryl, emetics and others that have been used to change the gastric function — are critically examined, and it is shown that their action on the stomach may be modified or reversed by the effect of the mental state present at the time; previous data about the length of time food remains in the stomach must be revalued in the light of the great changes that occur in emotional states. It is interesting that no effect from tobacco smoking on the motor activity, acid secretion or vascularity of the stomach was formed in the patient unless nausea appeared.

The wide range of the appearance of the healthy gastric mucosa is important in relation to the diagnosis of gastritis. The authors found the difference between hyperfunction of the stomach, however caused, and hypertrophic gastritis mainly one of degree: the protective action of gastric mucus is well shown. Some valuable and fundamental applications of this research are made in the treatment of gastritis and ulcer.

Three chapters have been added to the first edition of 1943, including further data on the effects of chemical agents and other influences on gastric function and the gastric mucosa, further correlation of gastric function with life situations (causing depression, resentment, anger, worry, fear, frustration and so forth) and a timely chapter on gastric studies of a patient with fistula both before and after vagotomy.

The book is very interesting, and no internist, practitioner or psychologist can afford to miss it. It ranks as a medical classic, and its significance has already been widely recognized.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Minor Surgery. By Frederick Christopher, M.D., associate professor of surgery, Northwestern University Medical School, and chief surgeon, Evanston (Illinois) Hospital. Sixth edition. 8°, cloth, 1058 pp., with 937 illustrations. Philadelphia: W. B. Saunders Company, 1948. $12.00.

This standard textbook, first published in 1929 and last revised in 1944, has been again thoroughly revised, and many sections have been entirely rewritten and new sections added. The material on the use of penicillin and other biotics and of the sulfonamides has been thoroughly revised in the light of present-day usage. The sections on thrombophlebitis and phlebothrombosis have been extensively revised and include consideration of anticoagulant therapy and femoral-vein ligation in the prophylactic treatment of pulmonary embolism. The sections on burns and varicose veins, pilonidal sinuses and methods of artificial respiration have been revised in the light of the knowledge gained from World War II. New material includes the control of hemorrhage by the gelatin sponge or oxidized cellulose, early postoperative ambulation, Lund's table of skin areas, procaine and serum sickness, plastic casts in burns, lumbar sympathetic block in thrombophlebitis, intra-arterial injection of penicillin and infections of the extremities, excision and enclosure of bedsores, treatment of malignant melanoma, prosthetic restoration of amputated finger, refrigeration anesthesia and the use of aluminum hydroxide paste in bowel fistula. The following sections have been amplified: wound healing, diet and burns, injection of novocain, and subacromial bursitis, Colles fracture, fractures of the carpal scaphoid, glomus tumors, novocain injections for ankle sprains, march fractures, sternal puncture, skin

grafting, the Rh factor, shock, fluid and electrolyte administration after operation, hypoproteinemia, use of the Miller–Abbott tube and pulmonary atelectasis. A selected bibliography is appended to each chapter, and a good index concludes the volume. The work is well published in every way and is recommended for all medical libraries and should prove of value to all persons interested in surgery.

The Sulfonamides and Allied Compounds. By Elmore H. Northey, Ph.D., administrative director, Stamford Research Laboratories, American Cyanamid Company, Stamford, Connecticut. 8°, cloth, 660 pp., with 323 tables. New York: Reinhold Publishing Corporation, 1948. $12.50.

This essential reference work covers the chemical side of the sulfonamide derivatives, simple and complex, the sulfones and their derivatives and other allied compounds. The structure and activities of the compounds are considered extensively. There are special chapters on the experimental evaluation and relation to structure of chemotherapeutic activity, pharmacology, theories of the mechanism of action and the clinical action of the drugs. In this fast expanding field over 5000 new compounds have been synthesized, and in 1943 the United States produced over 10,000,000 pounds of sulfonamides. The first two chapters deal briefly with the history of bacterial chemotherapy and nomenclature, classification and synthesis. A comprehensive bibliography of 2668 references concludes the text. The appendixes give a key of organisms or diseases, and the trade names for sulfanilamide, its derivatives and related compounds. The volume is well published in every way and is recommended for all medical libraries and to all physicians interested in chemotherapy.

A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology. By Torald Sollman, M.D. Seventh edition. 4°, cloth, 1132 pp. Philadelphia: W. B. Saunders Company, 1948. $11.50.

This standard work on pharmacology, first published in 1917, has been thoroughly revised to bring it up to date. In this revision the author has eliminated material no longer considered of real importance or interest. The text is printed in two columns and in two sizes of type. The large type presents material that should be known by all students, and the small type contains data for reference purposes. Since the publication of the last edition in 1942, there have been great advances in the field of pharmacology. Much material has been added throughout the volume, including the new antibiotic agents, the anti-infective sulfonamides, antimalarials, the antimonial drugs, the insecticides and rodenticides, the auxins and weed killers. The antithyroids, anticonvulsants, antihistamines, anticholine acetylases, folic acids, standardized curare digitoxin, nitrogen mustards and BAL are considered in the text. The extensive bibliography of 112 pages appended to the text comprises references to the pertinent literature published since January 1, 1926. The volume is well published and is recommended for all medical libraries and as a reference work for physicians.

The Industrial Environment and Its Control. By J. M. Dallavalle. 8°, cloth, 225 pp. New York: Pitman Publishing Corporation, 1948. $4.50.

This monograph in a new field of public health is well written, and the material well organized. Although technical in parts the text is kept as simple as possible and understandable to the average person. The monograph deals with engineering methods for the control of health hazards in factories. The first chapter discusses problems and trends, including the importance of industrial hygiene to the industrial physician and public-health administrator and the need for adequate reporting of morbidity and mortality. The various chapters consider psychrometry (the relation between temperature and humidity); air and its contamination; illumination and radiant energy; noise, vibration and fatigue; industrial ventilation in all its aspects; and industrial dust collection. An appendix discusses the general principles of industrial sanitation. Each chapter is documented with a list of pertinent references. The monograph is recommended for all public-health collections in medical and general libraries, in industrial plants and in health-department libraries of estates and cities, and to all persons interested in industrial sanitation. The printing is well done with a good type on good paper.

Hernia: Anatomy, etiology, symptoms, diagnosis, differential diagnosis, prognosis and treatment. By Leigh F. Watson, M.D. Third edition. 8°, cloth, 732 pp., with 323 illustrations. St. Louis: The C. V. Mosby Company, 1948. $13.50.

This authoritative work, first published in 1924, has been thoroughly revised in the third edition, and the type entirely reset. Chapters have been added on the complications of hernia, internal supravesical and epigastric hernias, hernia into the broad ligament, recurrent inguinal hernia and industrial hernia. Cooper's ligament operation, Babcock's operation for inguinal hernia using stainless steel wire and Harrington's operation for diaphragmatic hernia are described and illustrated in detail. Material has also been added on early rising after operation, suture materials, embolism and thrombosis, preoperative and postoperative treatment and new statistics on the rarer types of hernia. Much space has been devoted to a thorough consideration of nonoperative treatment by the injection method, including its use in inguinal, femoral, umbilical epigastric and ventral hernias. The bibliography has been brought up to date and appended to each chapter. Comprehensive indexes of authors and subjects conclude the volume. Many illustrations have been added. The printing is well done with a good large type on good coated paper. This paper is probably necessary to ensure adequate reproduction of the fine illustrations, but it makes the volume rather heavy to handle. The book is recommended as an essential reference work for all medical libraries and to all surgeons.

The Case Book of a Medical Psychologist. By Charles Berg, M.D. (Lond.), D.P.M., fellow of the British Psychological Association, physician of the British Hospital for Functional Mental and Nervous Disorders and physician to the Institute for the Scientific Treatment of Delinquency. 8°, cloth, 260 pp. New York: W. W. Norton and Company, Incorporated, 1948. $3.50.

Dr. Berg, in this second edition of his case book, has made a few minor changes and has substituted a long analytical case report for the three last articles in the section on war neuroses. All the papers were published originally in medical and psychologic periodicals. The text is written in a semipopular style and presents 34 cases, illustrative of the practical application of clinical psychology. Four cases of war neuroses are included for the purpose of demonstrating that these cases do not differ in any essential particular, except the ease of curability, from the average case treated by the clinical psychologist. The theoretical explanations attached to each case have been reduced to a minimum, but enough has been included to interest the general reader and prove of value to the practitioner of clinical psychology. In the last chapter the author discusses the theory and practice of psychoanalysis. The book is well published and should prove of value to all physicians interested in nervous and mental diseases.

Operative Gynecology. By Harry S. Crossen, M.D., consulting gynecologist to the Barnes Hospital, St. Louis Maternity Hospital, St. Luke's Hospital, de Paul Hospital and Jewish Hospital; and Robert J. Crossen, M.D., assistant professor of clinical gynecology and obstetrics, Washington University School of Medicine, assistant gynecologist and obstetrician to the Barnes Hospital and the St. Louis Maternity Hospital and gynecologist to St. Luke's Hospital and de Paul Hospital. Sixth edition. 4°, cloth, 999 pp., with 1334 illustrations. St. Louis: The C. V. Mosby Company, 1948. $15.00.

The first edition of this standard textbook was published in 1915, and the last edition in 1938. This new edition has been revised to bring it up to date, and to accommodate the large number of new data it was necessary to eliminate much of the historical material. This will make it essential for libraries interested in medical history to retain the fifth edition (1938) in their collections. Included in the new material are measures for the prevention of cancer, made a part of the sections on the various organs, and the development of measures for giving more effective relief to patients with general handicaps contraindicating operative removal of serious pelvic lesions. The volume is well published in every way. The many fine illustrations necessitate the use of a heavy paper, a fact to be deplored. The book is recommended for all medical libraries and should be in the collections of all gynecologists.

Modern Cosmeticology. By Ralph G. Harry, F.R.I.C., certificate of the Royal Institute of Chemistry in the Chemistry and Microscopy of Foods, Drugs and Waters, Pharmacognosy, Pharmacology and Therapeutics, and head of the Cosmetic Department, Beecham Research Laboratories, Ltd. With a foreword by P. B. Mumford, M.D., F.R.C.P. Third revised edition. 8°, cloth, 515 pp., illustrated. Brooklyn, New York: Chemical Publishing Company, Incorporated, 1947. $12.00.

This third edition of an unusual book has been enlarged and completely revised. The work deals with the practical and scientific aspects of cosmetic preparations and includes special investigations by the author and others in this field. In addition to skin preparations there is included material on dental, hair, nail and eye preparations. The sections on skin nutrition, sunburn and sun-tan preparations, allergy and dermatitis, histology and physiology of the nails and hair, diet and skin health should prove valuable to physicians. There are hundreds of formulas for the preparations described in the text, making the book invaluable to the dermatologist. The text is documented throughout with pertinent references. A good index concludes the work. The material is well organized, and the text well written in a simple, clear style. The type and printing are excellent. The heavy coated paper could have been dispensed with, since the few plates are inserts. The book is recommended for all medical and general libraries, and as a reference work for dermatologists and physicians.

Treatment by Diet. By Clifford J. Barborka, M.S., M.D., D.Sc., F.A.C.P., assistant professor of medicine, Northwestern University Medical School, attending physician, Passavant Memorial Hospital, and consultant in gastroenterology and gastroscopy, Diagnostic Centre, Hines Veterans Hospital. Fifth edition. 4°, cloth, 784 pp., with 14 plates. Philadelphia: J. B. Lippincott Company, 1948. $10.00.

This standard work, first published in 1934, and last revised in 1939, has been again brought up to date. More than half the volume has been rewritten, expanded or revised. Chapters on protein and amino acids, deficiency diseases, diet and skin diseases and on preoperative and postoperative dietary care have been added. New material on folic acid and on fat-soluble and water-soluble vitamins has been incorporated in the text. The chapter on liver disease has been rewritten to include the up-to-date use of protein, choline and other food factors in cirrhosis, chronic hepatic diseases and hepatocellular jaundice. In the chapter on diabetes mellitus the low carbohydrate diets have been eliminated and replaced by diets allowing up to 250 gm. A series of colored plates has been added to demonstrate the comparative servings of all types of foods recommended by the Food and Nutrition Board of the National Research Council. A long bibliography of thirty-eight pages is appended to the text, and there is a good index. The volume is well published and should be in all medical libraries and in the libraries of physicians interested in the subject.

Animal Genetics and Medicine. By Hans Grüneberg, Ph.D., M.D., reader in genetics, University College, London. With a foreword by Sir Henry Dale, O.M., G.B.E., F.R.C. 12°, cloth, 296 pp. New York: Paul B. Hoeber, Incorporated, Medical Book Department of Harper & Brothers, 1947. $5.50.

Dr. Grüneberg has confined his subject to the inherited diseases of laboratory rodents, omitting the domesticated animals, both large and small, because of the amount of space it would require for adequate coverage of the whole subject. Likewise, the subject of animal tumors has been omitted because it has been adequately covered in recent publications on cancer. The material is arranged according to the systems of the body, with special sections on the relation of animal to human congenital conditions. The beginning chapters discuss inherited diseases in general, the advantages and limitations in etiologic studies and the principles of developmental genetics. The two last chapters consider serology, including blood grouping, and disease resistance. A long bibliography concludes the text, and an attempt has been made to include wartime literature of Continental Europe. There are good author and subject indexes. The book is well published. The sheets were printed in Great Britain and bound in the United States. The author makes a plea for the proper utilization of material of interest to medicine now lying dormant in genetical periodicals seldom consulted by physicians. This unusual monograph should be in all medical reference collections.

NOTICES

ANNOUNCEMENTS

Dr. Robert B. Holden announces the opening of his office for the practice of internal medicine at 520 Commonwealth Avenue, Boston.

Dr. William D. Rowland announces the removal of his office from 180 Commonwealth Avenue to 140 Marlborough Street, Boston.

NEW ENGLAND CONFERENCE OF INDUSTRIAL PHYSICIANS AND SURGEONS

The next meeting of the New England Conference of Industrial Physicians and Surgeons will be held at the Copley Plaza Hotel, Boston, on September 22.

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY, INC.

A number of changes in Board requirements and regulations were made at the annual meeting of the Board held in Washington, D. C., May 16 to May 22. New bulletins are now available for distribution upon application and give details of all new regulations. These relate both to candidates and to hospitals conducting residency services for training.

The next written examination and review of case histories (Part I) for all candidates will be held in various cities of the United States and Canada on Friday, February 4, 1949.

Application may be made until November 1, 1948. Application forms and bulletins will be sent on request to the American Board of Obstetrics and Gynecology, 1015 Highland Building, Pittsburgh 6, Pennsylvania.

FEDERAL SECURITY AGENCY

Public Health Service
Washington, D. C.

Examination for Regular Corps

A competitive examination for appointment in the Regular Corps of the United States Public Health Service in the grade of assistant surgeon (first lieutenant) and senior assistant surgeon (captain) will be held in October. The written examination will be conducted October 4, 5, and 6 at places convenient to the candidates. The oral examination will be held at various points throughout the country.

All applicants must be at least twenty-one years of age and citizens of the United States, must present a diploma of graduation from a recognized medical school and satisfactorily pass a physical examination performed by Public Health Service officers.

Physicians beginning internship on July 1, 1948, will be admitted to the examination. Successful candidates will be placed on active duty in the Regular Corps upon completion of internship on July 1, 1949.

Applicants for the grade of assistant surgeon must have had at least seven years of educational and professional training or experience, exclusive of high school. Applicants for the grade of senior assistant surgeon must have had at least ten years of educational and professional training or experience, exclusive of high school.

Entrance pay for an assistant surgeon with dependents is $5011 a year and for senior assistant surgeon with dependents $5551 a year. This includes the additional pay of $1200 for medical officers, as well as subsistence and rental allowance. Provisions are made for promotions at regular intervals up to and including the grade of senior surgeon (lieutenant colonel) and for selection for promotion to grade of medical director (colonel) at $9751 a year. Retirement is authorized at either completion of thirty years' service or at the age of sixty-four. Full medical care including disability retirement at three-fourths pay is provided.

Application forms may be obtained from Public Health Service Hospitals, District Offices or by writing to the Surgeon General, United States Public Health Service, Washington 25, D. C.

(*Notices concluded on page xv*)